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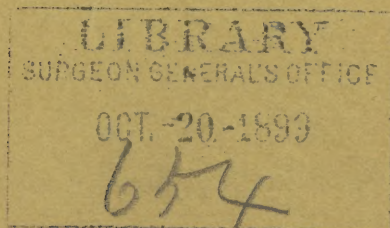
DIRECT AND REFLEX ACCELERATION OF THE
MAMMALIAN HEART, WITH SOME OBSERVA-
TIONS ON THE RELATIONS OF THE INHIBI-
TORY AND ACCELERATOR NERVES.

✓

presented by

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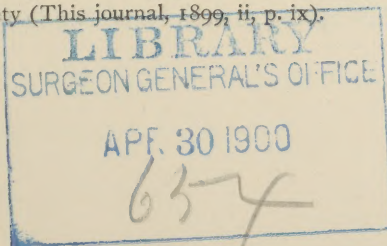
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¹ These experiments were performed in the Physiological Laboratories of the Johns Hopkins Medical School, and of the College of Physicians and Surgeons, New York; a summary of some of the results obtained was presented at the meeting of the American Physiological Society in December, 1898, and published in the Proceedings of the Society (This journal, 1899, ii, p. ix).



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PART I.

EXPERIMENTS ON THE ACCELERATOR NERVES.

Methods of investigation. — Most of the experiments described in this paper were performed on dogs, although some were made on cats and rabbits; it is to the dog, however, that the conclusions drawn are intended to apply primarily. The animals were always thoroughly anæsthetized in some manner. Curare was also frequently given; in these cases an effort was made to prevent the animal's temperature from falling during the experiment, either by warming the air (which was also saturated with aqueous vapor) or by keeping the animal on a zinc box filled with warm water. If during the course of an experiment the blood pressure became very low, intravenous injections of warm normal saline or of Ringer solution were frequently made; by means of such injections the blood pressure and heart rate could be kept near the normal for a long time, and results of value obtained from experiments which would otherwise have yielded none.

The heart rate and blood pressure were recorded by the mercury manometer in the usual manner; the readings of the blood pressure given have been corrected for the weight of the solution of sodium carbonate used to prevent coagulation of the blood. In some experiments Hürthle's spring manometers, connected either with an artery

or with a cannula passed into one of the ventricles, were extensively used.

The accelerators were usually exposed by resecting the first rib and opening the pleural cavities; such a procedure allows of a much more thorough exposure of the stellate ganglia and their branches than does the longer and more difficult method described by Schmiedeberg.

Full details of the individual experiments will be given throughout the paper.

TONIC ACTIVITY OF THE ACCELERATORS.

The views of physiologists seem to differ widely on the question whether the accelerator nerves are in a condition of tonic activity or not. In some of the leading English¹ and German² text-books on physiology the statement is made that these nerves are only occasionally, not continually, in a condition of activity. In other text-books both of physiology and of medicine and frequently in the writings of physiologists it is either stated explicitly that these nerves are usually in a condition of activity or the assumption is made that this is the case. Other authors again do not refer to the question at all.

Apparently the basis for the statement that the accelerators are not in a condition of tonic activity is the work of the Cyons.³ These physiologists, unlike von Bezold, failed to find any decrease in the heart rate in experiments on rabbits as a result of the section of the spinal cord or of the extirpation of the inferior cervical and stellate ganglia. The later investigations of Tschirjew,⁴ Stricker and Wagner,⁵ and of Timofeew,⁶ all agree in showing that these nerves

¹ WALLER: Introduction to human physiology, 3d ed., 1891, p. 107.

² LANDOIS: Lehrbuch der Physiologie des Menschen, 7th ed., 1891, p. 807.

³ CYON, M. and E.: Archiv f. Anat., Physiol., u. wiss. Medicin (Reichert and du Bois-Reymond), 1867, p. 406.

⁴ TSCHIRJEW: Archiv für Physiologie, 1877, p. 164.

⁵ STRICKER and WAGNER: Sitz.-Ber. d. kais. Akad. d. Wiss., 1878, math.-naturw. Cl., 77, Abth. III, p. III.

⁶ TIMOFEEW: Quoted in Centralblatt für Physiologie, 1889, p. 235. Timofeew did not observe any immediate effect upon the heart rate of cutting the accelerators; about three days after the operation, however, slowing of the heart began, and seems to have been permanent. That no immediate slowing of the heart occurred in these experiments may have been due to a reflex diminution of the tonicity of the vagi (which of itself would lead to an acceleration) resulting from

are usually in a condition of tonic activity in rabbits as well as in dogs; moreover E. v. Cyon himself, in a recent article giving the results of experiments performed for the most part upon rabbits, speaks as though he considers these nerves to be in a condition of tonic activity.¹

My own experiments, some of which have already been published,² lead me to believe that the accelerators must be considered as almost always in a condition of tonic activity, in fact much more constantly so than the cardio-inhibitory nerves.

So far as I know the only question in relation to the tonic activity of the accelerators discussed by previous writers is the effect of the section of these nerves upon the rate of the beat of the ventricle; this as well as some other problems will be discussed below.

Effect of the section of the accelerator nerves upon the heart rate; resistance of the accelerator centres. — I have very little to add to what I have said in my previous paper as to the effect upon the heart rate of cutting the accelerator nerves; in the large number of additional experiments which I have made, I rarely have found a case in which they were not in a condition of tonic activity. This was true whatever the drug used for anæsthesia, and when anæsthesia was produced not by drugs but by section of the crura cerebri or by compression of the cerebrum; also whether the vagi were intact or had been divided.

One criticism which may be made against some of the experiments upon the effect of cutting the accelerators should be referred to here. The operation necessary to expose thoroughly the accelerator nerves sometimes leads to a lowering of the mean blood pressure; since the work of v. Bezold³ and Tschirjew it has been generally believed that a low blood pressure acts of itself as a stimulus to the centre of

the operation; I have referred to this point in a previous paper (*Journal of experimental medicine*, 1897, ii, p. 160).

Hering (*Archiv f. d. ges. Physiol.*, 1895, lx, p. 468) observed an increase in the heart rate to follow extirpation of the stellate ganglia (the vagi being intact); after a few days the rate returned partially to the normal. Subsequent section of the vagi caused but little increase in the heart rate. These results seem also to indicate a tonic activity of the accelerators, the acceleration immediately following the operation probably being due to a diminution of the tonic activity of the vagi.

¹ VON CYON, E.: *Archiv f. d. ges. Physiol.*, 1898, lxx, p. 242.

² HUNT: *Journal of experimental medicine*, 1897, ii, p. 158.

³ VON BEZOLD: *Centralblatt f. d. med. Wissenschaften*, 1866, pp. 819, 820.

the accelerator nerves.¹ Unless this factor is taken into consideration the objection may be made that an abnormal stimulation of the accelerators by low blood pressure has been interpreted as tonic activity of the centre. There were however among my experiments many cases in which as a result of careful operation the blood pressure was high (probably very near the normal) when the accelerators were cut, and yet there was a very marked slowing of the heart. The following figures from an experiment upon a rather small dog may serve as an illustration of this point: the blood pressure was 130 mm. of mercury, the heart rate $39\frac{1}{2}$ in 10 seconds; section of the accelerators on the right side caused the blood pressure to fall to 122 mm., while the heart rate decreased to $26\frac{1}{2}$ beats in 10 seconds; section of the accelerators on the left side caused no change in the heart rate, but the blood pressure fell to 95 mm.

On the other hand I have in a few cases obtained results to which the above objection may properly be made. Occasionally an animal was found in which the accelerators seemed to be in a condition of maximum acceleration, that is, electrical stimulation of the nerves after their section did not cause the heart to beat more rapidly than it had been beating before their section; in all such cases the blood pressure was very low. An example of such an experiment will be given below.

Section of the accelerator nerves in my experiments seldom led to a marked lowering of the blood pressure; hence the criticism cannot be made against these experiments which the Cyon brothers made against the work of von Bezold. Von Bezold cut the spinal cord and attributed the slowing of the heart which followed to the cutting off of the accelerator impulses; the Cyons attributed it to the fall of blood pressure resulting from the dilatation of the blood vessels of the abdominal organs when the spinal cord is divided.

The resistance of the accelerator centre to influences which reduce or entirely abolish the irritability of other physiological centres is very marked. Thus, while the tonic activity of the cardio-inhibitory and of the vaso-motor centres is lowered by such drugs as chloral, chloroform, and ether, and by excessive amounts of curare, these drugs seem to have but little effect upon the accelerator centre. In

¹ ASP (Sitz.-Ber. d. sächs. Gesellsch. d. Wiss., math.-phys. Cl., 1867, p. 173) and NAWROCKI (Beiträge z. Anat. u. Physiol., Festgabe für C. Ludwig, 1874, p. 220), however, consider the acceleration in these cases to be due to a diminution of the tonic activity of the vagi.

one experiment upon a dog, for example, after a very large amount of curare had been injected into a vein, the blood pressure fell from 83 to 22 mm. of mercury, and section of the vagi and stimulation of their peripheral ends had no effect upon the heart rate; yet section of the accelerator caused the heart rate to decrease from 29 to 23 beats in 10 seconds. In another experiment the blood pressure was 27 mm.; section of the accelerators caused the heart rate to decrease from 36 to $26\frac{1}{2}$ in 10 seconds. The accelerators were also found to be in activity in an animal which had been under the influence of ether for five hours, and in others in which severe operations and great loss of blood had led to an extremely low blood pressure. In a few animals, however, the temperature of which had fallen very low, the accelerators were not found in tonic activity.¹

Although section of the accelerator nerves has seldom failed to cause a slowing of the heart, yet the extent of this slowing has varied widely in the different experiments; in exceptional cases the rate after their section has been but one half or less than the previous rate. To what extent the variability of the results was due to differences in individual animals and to what extent to other causes it is impossible to state. In the case of the inhibitory fibres to the heart it is not difficult to determine the influences (drugs, etc.) which increase or diminish their tonus, and in the same animal this tonus may vary within wide limits in short periods of time; in fact the cardio-inhibitory centre seems to be in a condition of very unstable equilibrium. The tonus of the accelerator nerves is not so easily affected; I have been unable to find any constant relation between such factors, *e. g.*, as the degree of anæsthesia, the condition of the blood pressure and of the respiration, etc., and the extent of the tonus of the accelerators, nor do I know of any grounds for supposing that this tonus undergoes changes comparable to those of the cardio-inhibitory centre. There are, moreover, indications that the condition of the heart itself plays a very important part in determining the effect of cutting the accelerators; it is even probable that

¹ The resistance of the peripheral endings of the accelerators is also remarkable. Thus stimulation of the spinal cord in the cervical region has caused a marked acceleration of the heart, although, as a result of excessively large doses of curare, the blood pressure was not affected. In the last stages of asphyxia, also, stimulation of the accelerators is effective, as has already been described by Bowditch. Even when the heart is dying and the ventricles have ceased to beat, stimulation of the accelerators will sometimes cause the latter to begin again. Cold, however, diminishes the irritability of the accelerators, as was observed by Baxt.

changes in this organ are of more weight in this connection than changes in the accelerator centre.

Effect of section of the accelerator nerves upon the duration of systole and of diastole. — The duration of systole and diastole was determined in the manner described by Hürthle¹ from the curve of carotid pressure recorded by the spring manometer. As this method will be referred to frequently in later parts of this paper a few words will be said about it here. Hürthle has shown that when tracings are taken with his manometers from the cavity of the left ventricle and from the aorta simultaneously the time elapsing between the appearance of the primary and the dicrotic waves of the aortic pulse curve is almost the duration of systole as determined from the curve of intraventricular pressure. Of course these curves do not coincide in time; the primary elevation in the curve of aortic pressure does not appear until after the beginning of the systole of the ventricle and the dicrotic wave does not appear until a short time after the end of the systole. The former period, that is, the time elapsing between the beginning of the systole and the occurrence of the primary elevation on the curve of aortic pressure, corresponds to the time during which the intraventricular pressure is rising, but is not high enough to force open the semilunar valves (the *Anspannungszeit*); the latter period corresponds to the interval which elapses between the closure of the semilunar valves and the appearance of the dicrotic wave. Hürthle found in a number of observations that these two periods were almost of equal length, and that therefore the duration of systole can be determined directly from the curve of aortic pressure by measuring the time interval between the primary and the dicrotic wave. He suggests that the duration of systole and diastole can be determined in a similar manner from the curves obtained by his manometer from other large arteries.

I have made use of the above method for determining the duration of systole and diastole in a number of experiments. A Hürthle spring manometer was connected with one of the carotids and the pulse recorded upon the smoked paper of a Hürthle kymograph; the speed of the latter was 100 mm. per second. A cannula was also connected with the femoral artery and the blood pressure recorded by a mercury manometer in the usual manner. In a number of experiments records of intraventricular and of aortic

¹ HÜRTHLE: Archiv f. d. ges. Physiol., 1891, xlix, pp. 65-67.

pressure were taken simultaneously, a spring manometer being connected with a catheter which had been passed down one carotid into the left ventricle,¹ while a second manometer was connected with the other carotid. Comparison of the curves obtained in this manner sometimes showed a somewhat greater discrepancy than was to be expected from Hürthle's description; still the differences were so slight that the error could as a rule be disregarded.

One difficulty in using the above method for determining the duration of systole and diastole should be mentioned: it not unfrequently happens that after some change in the heart rate or blood pressure (such, for example, as that following stimulation of the cardiac nerves) the dicrotic wave of the curve becomes so indistinct as to make exact measurements difficult or impossible. Most of the experiments, however, or at least parts of most of the experiments, gave very satisfactory results.

The following experiment shows the effect upon the duration of systole and diastole of cutting the accelerator nerves.

Experiment C. — Small dog, anæsthetized by sulphate of morphine and ether; curare. Stellate ganglia exposed. Left femoral artery connected with mercury manometer; left carotid with Hürthle's spring manometer.

Time.			Heart beats in 10 seconds.	Duration in seconds of		Blood pressure mm.
Hr.	min.	sec.		systole	diastole	
1	23—	0	30	0.165	0.165	46
		10	Branches of l. stellate ganglion cut.			
	24—	0		0.165—	0.170	46
	30—	0		0.160—	0.190	42
	32—	0	28	0.160+	0.185	34
		10	Branches of r. stellate ganglion cut.			
		20		0.160+	0.180	
		25		0.165	0.195	
		30		0.175	0.195	
33	0		26+	0.205	0.225	
	30		21½	0.230	0.245	
34			20½ ²	0.235+	0.270—	32
35				0.250	0.270+	31

¹ A silver male catheter was found most convenient for this purpose.

² The maximum heart rate caused by stimulation of the accelerators in this experiment was 31 beats in 10 seconds, *i. e.*, but very slightly greater than the heart rate before the nerves were divided. This was, therefore, one of the cases in which the accelerators were in a condition of almost maximal acceleration when they were cut.

The results obtained in the above experiment are better expressed in the form of a curve (Fig. 1) in which the ordinates represent the duration in 0.05 of a second of the systole and diastole of a single heart-beat at the end of each thirty seconds and the abscissæ represent periods of thirty seconds.

Parts of the tracing taken with the Hürthle manometer are reproduced in Fig. 2.

Inspection of the above table and curves shows that in this experiment section of the accelerators caused both systole and diastole to be prolonged, the prolongation of the former being relatively (*i. e.* as compared

with the previous rate) slightly greater than that of the latter. In nearly all of my experiments results similar to these were obtained; usually however the prolongation of the systole, though a con-

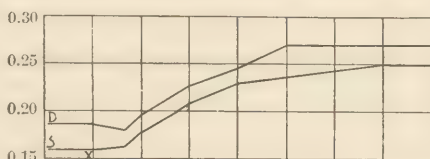


FIGURE 1. Experiment C. Accelerator nerves cut at *x*. *S* shows the duration of systole, *D* that of diastole in 5 hundredths of a second. The abscissæ represent periods of 30 seconds.

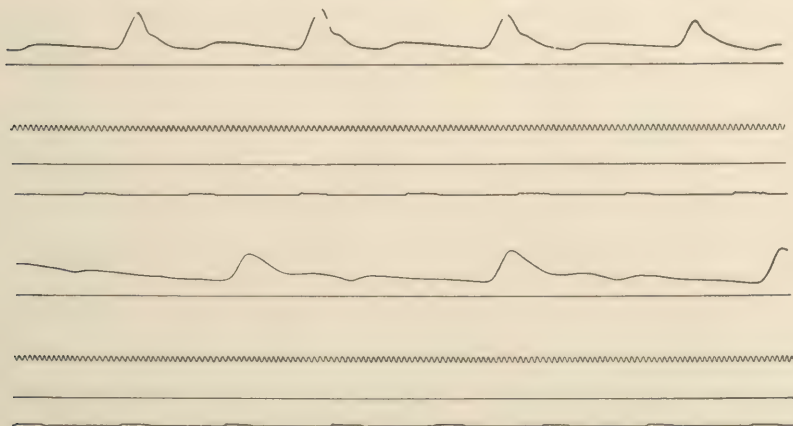


FIGURE 2. Two thirds the original size. Experiment C. Upper tracing before, lower tracing 2 minutes after, section of accelerators on right side. Time in intervals of 0.2 and 0.01 seconds.

stant result of cutting the accelerators, was not so marked as in this case.

The above experiment and the one quoted on p. 399, illustrate a point which I discussed in my earlier paper, namely, that section of

the accelerator nerves on the right side usually causes a more marked slowing than section on the left side.¹

Effect of section of the accelerator nerves upon the conduction of impulses from auricle to ventricle. — At least two experiments have been described which tend to show that the accelerator nerves contain fibres which affect especially the conduction of impulses from auricle to ventricle.² Certain observations have led me to think that these fibres are, under some circumstances at least, in tonic activity; or

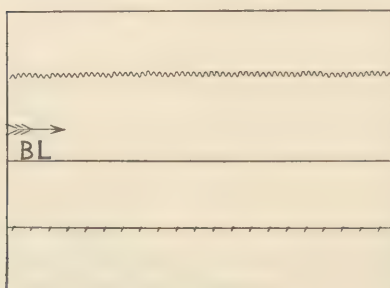


FIGURE 3. Two fifths original size. Experiment J. Curve of blood pressure before the accelerators were cut. *BL*, line of atmospheric pressure. Time in intervals of one second.

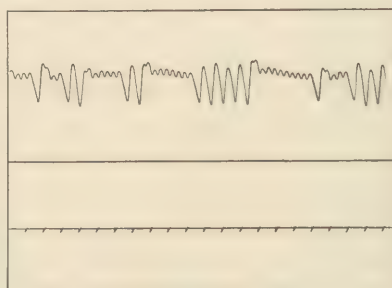


FIGURE 4. Two fifths original size. Part of the curve of Experiment J following Figure 3. Taken $4\frac{1}{2}$ minutes after the branches of the right stellate ganglion were cut.

perhaps it would be better simply to say that the tonic activity of the accelerators affects the conduction of impulses from auricle to ventricle as well as the rate of the heart.

The following is one of a number of experiments from which this conclusion is drawn.

¹ In most of my experiments in which the accelerators were stimulated on both the left and right sides, the latter caused greater acceleration than the former. Stricker and Wagner (*op. cit.*, p. 109) made the same observation. but François-Frank (Travaux du laboratoire de Marey, 1878-1879. iv, p. 83) failed to find any such differences in all but two of his experiments. — in these stimulation of the right accelerators caused a greater effect. These observations show that the distribution of the nerves varies in different individuals; but from my experiments I am convinced that, as a rule, more accelerator fibres pass to the heart on the right than on the left side.

² BAYLISS and STARLING: Journal of physiology, 1892, xiii. p. 407: HUNT and HARRINGTON: Journal of experimental medicine, 1897, ii. p. 725. In the present series of experiments I have often observed results similar to those described by Bayliss and Starling, namely, that stimulation of the accelerators after these nerves had been stimulated a number of times caused an acceleration of the auricles, but that the ventricles frequently failed to follow all of the auricular beats.

Experiment J. — Bitch, weighing 22.5 kilo. Anaesthesia produced by 4.8 grams acetone chloroform (trichloride of acetic acid) and a little ether. Curare. Vagi cut. A catheter had been passed down one carotid into the left ventricle and a record of intraventricular pressure taken. The right stellate ganglion and its branches were exposed. The blood pressure was 57 mm. of mercury; the pulse rate 30 in 10 seconds.

The accompanying curves (Figs. 3 and 4) show the effect upon the heart rate of cutting the accelerator nerves on the right side. The heart had been beating very regularly before the accelerators were cut; soon after they were cut there began to appear, occasionally, beats of unusual length. The number of these long beats increased very rapidly until finally there were periods of several seconds' duration in which the heart was beating at but one half its previous rate. The record of intraventricular pressure showed that this irregularity of the heart resulted from the "dropping" of some of the ventricular beats; that is, the duration of one of these long beats was just twice that of a normal beat. In some cases there was a slight, sudden rise of short duration of the intraventricular pressure during these long beats; this probably was due to the auricular beat.¹

The vagi had been divided in this experiment so that the change in the heart rate cannot be regarded as a reflex effect nor can it be attributed to changes in the blood pressure, for none occurred.

The auricular beats were not recorded, and therefore the following explanation of this irregularity cannot be considered as established with absolute certainty. But all observations seem to agree in showing that the ventricle when it suddenly begins to beat at one half its previous rate is responding to but every second auricular beat; the most probable explanation of the cardiac irregularity in the above experiment would seem to be that section of the accelerators had caused a diminution of the irritability of the muscle fibres connecting the auricle and ventricle. Of course another explanation may be offered, namely, that section of the accelerators had simply diminished the irritability of the ventricle so that it was unable to respond to all the impulses reaching it from the auricles. I think however that in the light of the work of Gaskell, MacWilliam, and Bayliss and Starling upon the conduction of impulses from the auricle to the ventricle, the former explanation is the more probable.

¹ Cf. HÜRTLE: *Archiv f. d. ges. Physiol.*, 1891, xlix, p. 55.

In other experiments upon dogs and cats and in one upon an opossum similar irregularities of the heart occurred after section of the accelerators, but as a rule they were less marked than in the experiment just described; in some, for example, a ventricular beat was dropped only occasionally. It is interesting that in all these cases it was section of the accelerators on the right side which led to these irregularities.

Inasmuch as the mammalian heart will continue under proper conditions to beat with great regularity for hours after it is entirely separated from the central nervous system, the question may be raised why in the above experiments section of the accelerators caused it to beat irregularly. It is quite probable that in these cases the irritability of the heart had been decreased in some manner to such an extent that the stimulus afforded by the accelerators was necessary to maintain regular cardiac action. In experiment J, for example, there were a number of influences which may have affected the heart. Thus the anæsthetic employed, acetone chloroform, seems to cause a loss of irritability of the heart, for in animals to which this drug has been given the heart rate is usually slow and the beat weak¹ after section of all the cardiac nerves; moreover, the blood pressure was low and perhaps the heart had been injured by the sound passed into the left ventricle.

In the other experiments also in which section of the accelerators led to cardiac irregularity there were conditions which make it probable that the irritability of the heart was abnormally low.

If the explanation offered above is the correct one, we should expect stimulation of the accelerators to cause the cardiac irregularity to disappear, especially as Bayliss and Starling² have shown that stimulation of these nerves makes the transmission of impulses from auricle to ventricle more easy; as a matter of fact electrical stimulation of the accelerators not only caused an increase of the heart rate but an entire disappearance of the irregularity. The latter also followed the intravenous injection of hot normal saline solution, an agent which undoubtedly increases irritability of the heart.

It is also interesting to note that in some of the exceptional cases in which section of the accelerators showed that they were not in tonic activity the heart was irregular both before and after all the cardiac nerves were divided.

¹ The injurious action of acetone chloroform upon the heart may be due to impurities which are usually found in specimens of this drug.

² BAYLISS and STARLING: *Journal of physiology*, 1892, xiii, p. 414.

From such observations and considerations as the above I think the conclusion may safely be drawn that at times the tonic activity of the accelerators is very important for the regular action of the heart.

FATIGUE OF THE ACCELERATOR NERVES.

The statement is frequently made that the accelerator nerves are not easily fatigued, but the only basis for this assertion with which I am acquainted is an observation by Böhm.¹ This investigator stated that he had stimulated the accelerators for two minutes without observing any indication of fatigue and expressed a doubt as to whether they can be fatigued at all. When it is remembered that even in cases of maximal acceleration the heart rate is rarely doubled, it does not seem reasonable to suppose that if any fatigue did occur it would be observed when these nerves were stimulated for so short a period as two minutes.

That these nerves are not easily fatigued when subjected to a moderate stimulation follows from the fact that they are in a condition of tonic activity; on the other hand it will be shown that fatigue may readily occur when the nerves are subjected to strong electrical stimulation. My experiments bearing on this point will be discussed in two parts; the first will be entirely descriptive, in the second an effort will be made to ascertain so far as possible where the fatigue occurs.

Changes in the rate of the heart-beat. — When the accelerator nerves are stimulated continuously for some time (ten minutes for example) the heart does not remain long at the maximum rate but shows a tendency to return to the rate at which it was beating before the stimulation began. If these changes in the heart rate be expressed in the form of a curve in which the abscissæ represent the time and the ordinates the number of heart-beats in a given time (*e. g.* ten seconds) it will be found that as a rule the decrease in the heart rate occurs in two periods. There is first a comparatively rapid fall in the curve; this is followed by a much longer period in which the descent is very slight. Under some circumstances — these being determined by the condition of the heart and nerves, the character of the stimulus employed, etc. — the curve is continued in an almost straight line during the second period; in other words, the heart continues beating throughout this period at nearly a constant rate. The dura-

¹ BÖHM: Archiv f. exper. Pathol. u. Pharmakol., 1875, iv, p. 275.

tion of these two periods is very variable; occasionally they are absent altogether, there being in this case either no decrease at all in the heart rate (if the stimulation is of comparatively short duration) or the heart rate may decrease regularly; *i. e.*, the curve becomes an almost straight line.

The following experiment and curve show the usual result of stimulating the accelerators continuously for some time.

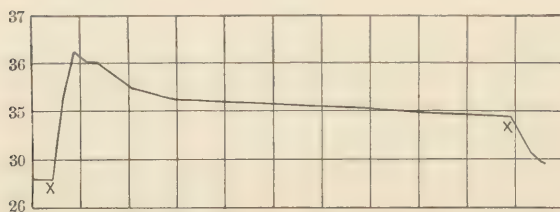


FIGURE 5. Experiment 117. Stimulation of the accelerator nerves for $9\frac{1}{2}$ minutes (x to x). The ordinates represent the number of heart-beats in 10 seconds; the abscissæ periods of one minute.

Experiment 117.

Small dog. Morphine and ether. Accelerators and vagi cut. The accelerators had been stimulated a number of times with results very similar to those shown in Fig. 5.

Curves similar to the above are nearly

always obtained when the accelerators are stimulated, whatever the condition of the heart or the strength or character of the stimulus employed. The same form of curve is also obtained in whatever part of their course the nerve fibres are stimulated, whether in the spinal cord, the rami communicantes, the annulus of Vieussens, or the small nerves running directly from the inferior cervical or the stellate ganglion to the cardiac plexus. When the same nerve is stimulated a number of times in succession there is a gradual lowering of the height of the curve, but the form remains the same; the latent period also becomes longer with the successive stimulations.

The above results recall those obtained when the peripheral end of the vagus is stimulated: in this case the heart, after a short period during which it is stopped or slowed, tends to return partially to its previous rate; it often reaches a constant rate, at which it continues to beat for hours.¹ Martin² found that when the isolated mammalian heart is warmed the beat is at first increased in frequency, but presently the heart returns partially to the former frequency and continues beating at this slower rate; in fact, if his results were

¹ See HOUGH: *Journal of physiology*, 1895, xviii, p. 176; also LAULANIÉ: *Comptes rendus de l'académie des sciences*, 1889, cix, p. 408.

² MARTIN: *Physiological papers*, 1895, p. 104.

expressed as a curve, the latter would have very nearly the same form as that obtained when the accelerator nerves are stimulated. Martin also called attention to the fact that similar changes in the heart rate are observed in some cases of fever—that is, the rate tends to return to the normal although the temperature remains the same.

When the accelerators are stimulated in the course of a long continued stimulation of the vagus, the curve of fatigue is the same as when they are stimulated alone.¹

Effect of the strength of the stimulus upon the course of fatigue.—The effect upon the heart in any given case of stimulating the accelerators with currents of varying strength and rate seems to be determined largely by the condition of the heart and nerves at the time of stimulation. If the heart is vigorous and the nerves have not been stimulated often it may be said that in general the stronger the current, the longer continued is the phase of maximal acceleration; if on the other hand the heart is not very vigorous or the nerves have been stimulated a number of times, fatigue occurs more quickly with a strong than with a weak current although the maximal rate reached by the heart may be the same in both cases. Also as a rule the stronger the stimulus the higher is the level at which the heart continues to beat during the stimulation.

It is interesting that a slight initial decrease in the heart rate occurs when the accelerators are stimulated with a current too weak to cause a maximum acceleration; this resembles the “escape” observed by Hough when slight slowing was caused by stimulation of the peripheral end of the vagus.

Effect of the rate of stimulation upon the fatigue of the accelerators.—The rate of the stimuli applied to the accelerators seems to have a greater effect upon the course of fatigue than does their strength. This was shown in many experiments in which the primary circuit of the du Bois-Reymond induction coil was interrupted by Ludwig's *Schlagwähler* or by an “oscillating rod” kept in vibration by an electromagnet; the number of stimuli per second could be varied within wide limits by either of these instruments.

The following experiment shows how much more quickly fatigue is produced with a rapid rate of stimulation than with a slower rate.

¹ An experiment illustrating this is given on pages 174 and 175 of my article in the *Journal of experimental medicine*, 1897, ii.

Experiment 137.—Dog. Morphine and ether. Curare. Spinal cord cut in mid cervical region. Branches of stellate ganglia divided. The result of stimulating the accelerators is shown in the following table.

Time.		Heart-beats	Time.		Heart-beats
Hrs.	min.	in 10 seconds.	Hrs.	min.	in 10 seconds.
3	41	11	55	Secondary coil 10 cm.	17+
	R. annulus stimulated;	14—			—
	primary circuit inter-	21½+			20+
	rupted 5+ times per	20½	56		20+
	second; secondary	19—		Coil 5 cm.	—
	coil 13 cm.	16½			—
42		— ¹			20+
	Stimulus off annulus.	16½	59		20—
		—		Coil 0 cm.	—
		16½—			—
		16½			20
		16	4	2	20
3	53			5 stimuli per second;	—
	R. annulus stim.; 2½	12—		coil 0 cm.	21—
	stimuli per second;	—			—
	secondary coil 13 cm.	16+			18+
		—			17½
		17—	4		17
		—			

In the above experiment no diminution of the acceleration occurred when the accelerators were stimulated with 2½ stimuli per second, whereas 5+ stimuli per second caused such a diminution to occur very quickly.

In almost every experiment there was found a rate at which the accelerators could be stimulated for some time with but little decrease in the acceleration. This, which may be called the optimum rate, varied greatly in different experiments and seemed to be determined by the condition of the heart and nerves. Thus in one experiment stimulation of the right annulus with an ordinary du Bois-Reymond coil in which the primary circuit was interrupted by the Neef hammer, caused the heart rate to increase from 23 to 29 beats in 10 seconds; but in the course of three minutes during which the stimulation continued the rate decreased to 24½+: after a few minutes' rest the annulus was again stimulated but now the primary circuit of the coil was interrupted by the *Schlagwähler* at the rate of 6 times per second; the rate of the heart increased from 22 to 29½ beats in 10 seconds; after three minutes' stimulation the rate was 29, showing that no fatigue had occurred.

¹ The dash (—) indicates that the heart-beats were not counted for 10 seconds.

Duration of systole and diastole in fatigue. — A number of experiments was made to determine whether both systole and diastole became longer when fatigue occurred in the course of a prolonged stimulation of the accelerators; it was found that they were longer, and that the prolongation occurred to about the same extent in both cases, so that the curve representing these changes were almost parallel.

It is interesting to compare these results with those observed when the heart is "escaping" during a prolonged stimulation of the vagus. When the peripheral end of the vagus is stimulated the diastole is always prolonged; as a rule the systole is also prolonged, but to a less extent; but while the diastole becomes shorter as the heart "escapes" to a more rapid rate, the systole remains about the same length throughout the stimulation. Thus during the "escape" of the heart from slowing as well as during the slowing caused by stimulation of the vagus it is the diastole which is most easily affected. On the other hand when the heart is slowed by section of the accelerators or when it is accelerated by the stimulation of these nerves or when fatigue occurs during their stimulation, both systole and diastole are affected; in fact, it seems almost as if one was affected through the other. If however the accelerators are stimulated when the heart is beating very slowly, as a result for example of stimulation of the vagus, then shortening of the diastole may occur before that of the systole; this point will be referred to later.

Local effects in the nerve. — It became evident very early in the investigation of the cause of the decrease in the heart rate during a prolonged stimulation of the accelerators that two factors are involved; first, a local action upon the nerve at the point stimulated, and, secondly, an effect upon the heart itself or upon the nerve endings in the heart. The latter effect is the more interesting in this connection, but it is necessary to consider the former or a serious error will be introduced into the experiment.

Local effect upon the nerve at the point of stimulation. — Howell¹ has shown that when certain nerves, especially some of the non-medullated variety, are stimulated with the faradic current for some time there occurs a loss of irritability at the point of stimulation; he called this loss of irritability "stimulation fatigue," without however expressing any opinion as to its real nature.

¹ HOWELL, BUDGETT, and LEONARD: *Journal of physiology*, 1894, xvi, p. 311.

This local effect of the current upon the nerve is easily demonstrated in the case of the accelerators. If the stimulating electrodes be held on one point of the nerve until the heart rate has begun to decrease and they then be moved a few millimetres nearer the heart, a second increase in the heart rate occurs; this, like the first acceleration, continues a short time and then the heart rate again decreases. This experiment may be repeated a number of times.

The following experiment will serve to illustrate this point.

Experiment 119. Dog. Morphine and ether; curare. Accelerators and vagi cut. Blood pressure 82 mm.

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
5 20 30	28½	26 20	36
Stimulation of r. an- nulus begun; sec- ondary coil 17 cm.		27	34½
40	32+	Electrodes moved slightly.	
21	40+	20	39+
22	37½+	28	37½
25	32½	30	34
26	31	Electrodes moved slightly.	
Electrodes moved slightly.		20	38½

In the above experiment the electrodes were moved towards the heart, but the same result is obtained when they are moved farther away from the heart,—a fact which shows that the conductivity of the nerve fibres at the point of stimulation is not lost.

If instead of moving the electrodes to a different part of the nerve after the acceleration has begun to decrease, the strength of the stimulating current suddenly be increased, the pulse rate may again be accelerated for a short time. By increasing the strength of the stimulus repeatedly at short intervals the heart may be kept beating at the maximal rate for some time.

Effect of stimulating the accelerators in different parts of their course.—Howell has shown that it is in the non-medullated nerve fibres that this local loss of irritability most often occurs, while the medullated fibres are less subject to it. In view of these results it is of interest to compare the effects of stimulating the accelerator nerves in that part of their course in which they are medullated with those observed when they are stimulated at a point where they are non-medullated. According to the prevailing view, these nerve fibres

belong to the medullated variety while passing from the spinal cord through the rami communicantes to the stellate, inferior cervical, and perhaps other ganglia of the sympathetic system; from these ganglia they are continued as non-medullated fibres to the cardiac plexus. According to this view, therefore, in order to compare the effects of stimulating the medullated and non-medullated accelerator fibres we have only to stimulate the spinal cord or the rami communicantes on the one hand and the small nerves passing from the annulus and the inferior cervical ganglion on the other. The annulus itself probably contains both medullated and non-medullated fibres.

It has been already stated that the form of the curves of fatigue was the same in whatever part of their course the nerves were stimulated; it is impossible in most of the experiments, however, to state whether the fatigue occurred in the heart or was a local effect upon the nerve, as at the time no special attention was given to this point. The following experiment indicates, however, that the local effect upon the nerves varies according to the part of the course in which they are stimulated.

Experiment 125. Dog. Morphine and ether. Right accelerators cut. Vagi intact.

The second thoracic ramus communicans had been stimulated a number of times, during and probably as a result of which the heart rate had decreased from 34 to 22 beats in 10 seconds. The right annulus was now stimulated for the first time, with the result shown in the following table.

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
12 40 30	22½—	43	26½
R. annulus coil 16 cm.	26½+	46	25
	35—	40	Current turned to 2d ram. com.
	35+	47	36
	35+	48	34½+
41 30	31—	49	33+
42	27+	52 40	30½
30	26½+		

Thus during a stimulation of the right annulus continuing 6 minutes the heart rate fell to 25 beats in 10 seconds, while during a stimulation of the ramus communicans of the same duration it fell to but 30½ and this notwithstanding the fact that the latter nerve had been stimulated a number of times while the former was stimulated

for the first time and that also a much larger number of accelerator fibres was doubtless stimulated when the current was applied to the annulus than when the ramus was stimulated. The explanation of the above difference is probably to be found in the fact that the nerve fibres in the ramus are medullated while many at least of those in the annulus are non-medullated.¹

There is also a difference in the rapidity with which the different accelerator nerve fibres recover their irritability after stimulation. Thus in the above experiment stimulation of the annulus after 20 minutes' rest caused an acceleration of from 23 to but 26 beats in 10 seconds, whereas stimulation of the second ramus after a rest of 20 minutes caused the heart rate to increase to 35 in 10 seconds.

Fatigue occurring in the heart as a result of stimulating the accelerators.—While the experiment described above shows that the decrease in the heart rate occurring after a prolonged stimulation of the accelerators is due in part to a local action upon the nerve fibres at the point of stimulation, there is very clear evidence that the heart itself can be fatigued by excessive stimulation of these nerves. That the heart is not easily fatigued by stimulation of the accelerators follows from the fact that they are usually in a condition of tonic activity; it was also shown above that moderate electrical stimulation, especially stimulation with a weak, slowly interrupted current, does not easily cause fatigue. If, however, the electrical stimulation is excessive or often repeated, and especially if the heart has been subjected to injurious influences, distinct indications of fatigue in the heart² occur, as will be shown below. It is very probable that

¹ Similar results were obtained in a few experiments in which the spinal cord and the accelerator nerves were stimulated; most of these experiments, however, were complicated by an unexpected factor. In a number in which the spinal cord had been divided in the cervical region not only was the acceleration from stimulation of the cord and of the accelerators very slight, but fatigue occurred with extraordinary rapidity. The section of the cord seemed to reduce the irritability not only of the accelerator fibres in the cord, but also of those in the annulus and the branches of the stellate ganglia. Munk and Schultz (*Archiv für Physiologie*, 1898, p. 307) have observed a similar loss of irritability in the phrenic nerve after section of the spinal cord; one explanation which they suggest, with considerable reserve, is that the irritability of the nerve was affected by the changes in the circulation following section of the cord. It is doubtful whether this explanation would hold for the accelerators: for, as has been pointed out above, these nerves are not easily affected by changes in the blood pressure.

² The expression "fatigue in the heart" is meant to include either fatigue of the endings of the accelerator nerves or of the cardiac muscle, or of both; it is by no means easy in many cases to distinguish between the two.

the same thing occurs whenever the accelerators are thrown into excessive action by causes originating in the body itself.

Effect of repeated stimulations of the accelerators upon the pulse rate, irritability of the heart, etc.—After repeated stimulation of the accelerators the pulse rate very often decreases. This decrease frequently occurs in cases where the vagi have been cut and therefore it cannot always be referred to an increased influence of the inhibitory nerves; nor can it in many cases be due to changes in the blood pressure or to a decrease in the animal's temperature, for it takes place when no such changes occur. Moreover in many experiments no change in the heart rate occurs during periods of rest of the same duration as the periods of stimulation. From such considerations as these I think the conclusion must be drawn that the slowing of the heart following stimulation of the accelerators is due to fatigue of the heart itself.

The following data may serve as an illustration of the extent to which the heart may be slowed as a result of repeated and long continued stimulation of the accelerators. The experiment was performed upon a dog anæsthetized by morphine and ether. After section of the vagi and accelerators the heart rate was 40+ in 10 seconds. The accelerators were stimulated 39 minutes; soon after the stimulation the rate was 34 in 10 seconds and it remained at this level during the period of rest which followed the stimulation. After a second stimulation of the accelerators continuing 9 minutes the heart was beating at the rate of 28 in 10 seconds and continued at this rate during a period of 5 minutes' rest. The nerves were now stimulated a third time. The stimulation continued only five minutes, but after it the rate sank to 22½. During this entire period the blood pressure had fallen very slightly, only about 10 mm. of mercury.

Results similar to the above are often observed, but it is not always so easy to exclude factors other than that of the stimulation of the accelerators.

That the irritability of the heart is lowered by long continued stimulations of the accelerators is shown by such an experiment as the following; the animal used was a dog anæsthetized by morphine and ether. Early in the experiment a small branch of the right annulus was stimulated for 20 seconds; the heart rate increased from 20 to 33 in 10 seconds. The ventral limb of the right annulus was now stimulated for 21 minutes, the position of the electrodes upon

the nerve being frequently changed. After the cessation of the stimulation the small branch of the annulus mentioned above was stimulated again with the same strength of current as before: the heart rate increased from 20 to but $25\frac{1}{2}$ in 10 seconds. The only plausible explanation of the slight effect caused by the second stimulation of this small nerve is that the irritability of the heart had been diminished by the long continued stimulation of the annulus.

Numerous other cases could be quoted in which stimulation of the annulus or of the small branches passing from the inferior cervical ganglion had but little effect upon the heart after repeated or long continued stimulation of the spinal cord or of those rami communicantes through which the accelerator fibres pass.

Another indication that stimulation of the accelerators causes a diminution of the irritability of the heart is found in the study of the effects of the intravenous injection of extracts of the suprarenal gland. As is well known, the injection of such extracts into an animal in which all the cardiac nerves have been cut leads to a great acceleration of the heart-beat; in a number of my experiments the maximum rate reached after such an injection coincided almost exactly with the maximum rate resulting from stimulation of the accelerators. Small quantities of the extract may be injected a number of times in succession without any diminution of the effect. If, however, the accelerators be stimulated for some time with a strong current between two such injections, it is found that the second injection has less effect than the first one. Thus, early in one experiment stimulation of the right annulus caused an acceleration from $31\frac{1}{2}$ to $40\frac{1}{2}$ beats in 10 seconds, while the injection of an aqueous extract of the suprarenal of a dog caused the heart rate to increase to 39. The accelerators were now stimulated for about an hour, and then after a period of rest they were again stimulated for a short time; the result of the second stimulation was that the heart rate increased from 31 to $35\frac{1}{2}$ beats in 10 seconds; the injection of the same quantity of the suprarenal extract as above caused the heart rate to increase to 35.¹

¹ The interpretation of these results will depend upon the view held as to the action of suprarenal extracts upon the heart. If we accept the view of v. Cyon (*Archiv f. d. ges. Physiol.*, 1898, lxxii. p. 371) that these extracts act upon the endings of the accelerator nerves, these experiments can only be regarded as evidence that the stimulation of the accelerators caused fatigue of the endings of these nerves; if, however, we adopt the view of Cleghorn (*This journal*, 1890, ii. p. 281), based upon experiments with the isolated apex of the dog's heart, that the

In another experiment suprarenal extract caused a marked acceleration before the accelerators were stimulated; after the nerves were stimulated until they ceased to have any effect upon the heart another injection of the suprarenal extract was made, but with entirely negative results.¹ At times on the other hand the injection of suprarenal extract seems to restore the influence of the accelerators over the heart.

Two other results of repeated stimulations of the accelerators which probably indicate a loss of irritability of the heart may be mentioned: first, the latent period of acceleration is prolonged, and secondly, the after-effect of the stimulation is much less marked, *i. e.*, the heart returns much more quickly to its previous rate after stimulation of the accelerators.² This rapid return of the heart to the

action of these extracts is upon the cardiac muscle itself, then I think my experiments can be regarded as evidence that the heart muscle is fatigued by stimulation of the accelerators.

¹ There are other points of similarity between the action of the accelerators and suprarenal extracts. Thus it has been my experience that when stimulation of the former from any cause failed to cause an acceleration of the heart, injection of the latter was also without effect. The effect of repeating the injections at short intervals is, moreover, very much like that of moving the electrodes slightly during a long continued stimulation of the nerves; after each injection, as after each shifting of the electrodes, there is a fresh increase in the heart rate. The heart can be kept beating at the maximum rate for some time in this manner.

It is also interesting to note in this connection that it was impossible to obtain any summation of the effect of the maximal stimulation of the accelerators and of the injection of suprarenal extracts; thus, when the injection was made simultaneously with the stimulation, the maximum rate of the heart was no greater than when it was made alone or when the accelerators were stimulated alone. If, however, the stimulus applied to the accelerators was sub-maximal, the injection of suprarenal extract would cause the heart rate to reach the same level as when the stimulus was maximal or when a considerable amount of extract was injected alone. There seemed to be a limit to the rate to which the heart could be accelerated (just as in cases of Basedow's disease, fever is said to cause no farther acceleration of the heart); in these experiments this limit was the same for the injection of suprarenal extract and for the electrical stimulation of the accelerators. It may be added that in one experiment injection of warm Ringer solution caused the same acceleration as did stimulation of the spinal cord and of the annulus.

Böhm states that in cats certain drugs cause a greater increase in the heart rate than does stimulation of the accelerators, and that therefore the acceleration of the latter case is not maximal; it should be noted, however, that these comparisons were not made upon the same animal.

² BÖHM (Archiv f. exper. Pathol. u. Pharmacol. 1875, iv, p. 275) made a similar observation, but did not offer any explanation of it.

previous rate is especially marked if the irritability of the heart has been reduced by the action of cold as well as by repeated stimulation of the accelerators.

Stimulation of the vagus after repeated stimulation of the accelerators.—I think further evidence of fatigue occurring in the heart as a result of stimulating the accelerators is to be found in the comparison of the effects of stimulating the vagus before and after repeated stimulations of the accelerators. We know from the experiments of Hough¹ (and I have had many opportunities of confirming his results) that the less vigorous the heart the greater is the effect of the stimulation of the vagus. Hence if stimulation of the accelerators does reduce the vigor of the heart we should expect to find the effect of the vagus increased after a long continued stimulation of these nerves; experiment shows this to be the case. This result is shown in a striking manner if, as was the case in the following experiment, the accelerators are stimulated during a prolonged stimulation of the vagus.

Experiment of July 2d. Bitch. Morphine and ether; curare. Vagi and accelerators cut. The accelerators had been stimulated a number of times with the result that the maximum acceleration was less with each successive stimulation. The following table shows that the effect of the vagus became greater after stimulation of the accelerators.

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
4 22	40	24	36½
	Stimulation of r. vagus begun; 13 stimuli per second; second- ary coil 0 cm.	25	31
10	27	26	24+
20	23+	4 26 10	24
23	25	30	21
	Stimulation of r. annu- lus begun; second- ary coil 17 cm.		R. annulus stimulated; secondary coil.
10	32½	27 10	24½+
20	41	28	23½
30	41½	29	18
		35	38
			Stimulus off annulus.
			Stimulus off vagus.

In this experiment the slowing of the heart caused by stimulation of the vagus became greater after each stimulation of the accelerators. That this was due to a change in the heart resulting from the stimulation of the accelerators is shown by the fact that when

¹ HOUGH: Journal of physiology, 1895, xviii, p. 162.

the vagus was stimulated alone the heart rate tended to return to the normal rather than to become slower; an indication of this tendency is shown in the first part of the above table.

In another experiment very similar to the above, stimulation of the vagus caused the heart to be slowed from 27 to $17\frac{1}{2}$ beats in 10 seconds; after a stimulation of the accelerators of but 28 seconds' duration stimulation of the vagus caused the heart to be slowed to 11 beats in 10 seconds. It should be added that in order to show the greater efficiency of the stimulation of the vagus after stimulation of the accelerators the former must follow the latter immediately, that is, the diminution of the irritability of the heart is of short duration unless the stimulation of the accelerators is continued for a long time.

If the vagi are intact and in tonic activity the slowing following stimulation of the accelerators seems to be due in part to an increased influence of the vagi over the heart, for the slowing occurs much more quickly in experiments in which the vagi are intact than in those in which they have been divided.

Such experiments as those just described seem to me to be of special interest and importance since they seem to show very clearly that stimulation of the accelerators causes diminished irritability of the cardiac muscle and not simply fatigue of the endings of the accelerator nerves; it is very difficult in most cases in which there are indications of fatigue in the heart to distinguish between these two possibilities.

Effect of some drugs upon fatigue of the accelerators.—The results of a few observations which I have made incidentally upon the effect of two or three drugs upon the occurrence of fatigue from stimulation of the accelerators may be referred to here.

After the intravenous injection of large doses of atropine and curare stimulation of the accelerators causes very rapid fatigue; whereas after the injection of sodium iodide¹ the fatigue is much less marked and the same is apparently the case after the injection of extracts of the suprarenal glands.

The following experiment illustrates the effect of a large dose of curare and of the injection of sodium iodide.

¹ The use of sodium iodide was suggested to me by the work of Barbèra (*Archiv f. d. ges. Physiol.*, 1897, lxxviii, p. 436) and v. Cyon (*Ibid.*, 1898, lxii, p. 176), who found that this salt acts as a powerful stimulus to the vasomotor and accelerator nerves; it also increases the irritability of these nerves while markedly lowering that of the vagi.

Experiment 148. Dog. Morphine and ether. A very large amount of curare was injected into the femoral vein as a result of which the blood pressure had fallen from 83 to 20 mm. of mercury: it rose later to 22 mm. The accelerators on the right side had been divided. The results are given in the following table.

Time.			Heart-beat in 10 seconds.	Blood pressure.
Hrs.	min.			
1	50		21+	22
		R. annulus stim. for 70 sec., coil 14 cm.		
			33	
			32	
			30	
			25½	
			23	
		(Record not good for 20 seconds.)	?	?
		Stimulus off annulus.		
			19	
	53		20	21
		5.2 ccm. 20% sol. NaI in- jected into femoral vein.		
	54		20	19 ¹
		R. annulus stim. as above.		
			27	
			32	
			?	
			29½	
			29+	19
			29+	
			29+	
1	55		29+	
		Stim. off annulus.		
			27½	
			26½	
	56		28	

The experiment was continued for 25 minutes, during which the accelerators were stimulated a number of times with results very similar to the above, *i. e.*, there were very slight indications of fatigue.

The fatigue caused by stimulation of the accelerators is also less after the intravenous injection of warm Ringer solution; the acceleration is also greater. Thus in one experiment stimulation of the spinal cord, which had been divided in the upper cervical region,

¹ As a rule the injection of sodium iodide causes first a fall and then a rise of blood pressure; that this did not occur in this experiment was probably due to the action of the very large dose of curare.

caused an acceleration from 19 to 25 beats in 10 seconds but this rate was maintained for but a very short time. After the intravenous injection of 400 c.c. of warm Ringer solution, which caused the blood pressure to increase from 27 to 61 mm. of mercury, stimulation of the cord caused an acceleration to 29 beats in 10 seconds and there was very little evidence of fatigue when the stimulation was continued for some time. Of course the greater efficiency of the stimulation of the accelerators may have been due in part to the higher blood pressure.

A large amount of atropine suddenly injected into a vein causes the heart (or the endings of the accelerators) to be fatigued by stimulation of the accelerators almost as rapidly as did curare in the above experiment.

Death from stimulation of the accelerators. — It happened not unfrequently that death resulted from stimulation of the accelerators in these experiments. This usually occurred after a long experiment in which the accelerators had been stimulated repeatedly with strong currents or after the irritability of the heart had been reduced by the action of curare or of cold. Sometimes the ventricle suddenly went into fibrillar contractions either during or immediately after the stimulation of the accelerators, in other cases the heart-beats became slower and weaker until they were no longer recorded.

An example of the latter mode of death is the following.

Experiment 120. Small dog. Morphine and ether. A very large amount of curare was injected into the femoral vein, as a consequence of which the blood pressure fell to 27 mm.

The results of stimulating the accelerators are shown in the following table.

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
3 45	24½	48	25
	R. annulus stimu-	50	23—
	lated; coil 14 cm.	52	20
20	37	54	12½—
30	38½	55	12½
47	33	56	11

The heart became so weak that the beat was not recorded ; it soon stopped altogether.

Death caused by fibrillar contractions, together with the effect of cold on the heart, is well illustrated by the following experiment.

Experiment 147. Small bitch. Morphine and ether. Vagi cut. A small opening was made in the pericardium and a considerable quantity of normal saline solution at about 10° C. injected; the heart was slowed slightly for a short time and then it returned to its previous rate (31 in 10 seconds).

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
3 54	31	4 10	23
Branches of r. stellate ganglion cut.			23+
	15½	R. annulus stimulated; secondary coil 12 cm.	24+
55	12		27½
	12		30+
56	24		29+
Normal saline (10° C.) injected into pericar- dial cavity.			28
	23½		24
	22½+	Ventricles going into fibrillar contractions; auricles beating regu- larly.	
57			
Branches of l. stellate ganglion cut.			

Death from stimulation of the accelerators frequently occurred with as much suddenness as in the above experiment, although in those cases in which the accelerators had been stimulated repeatedly the heart rate had as a rule decreased somewhat (from 28 to 19 in one experiment, for example).

Sometimes the heart beat regularly and rapidly during a stimulation of the accelerators but died a few seconds after the stimulations ceased.

The strength of the current used in these experiments in which death occurred was no greater than that used in other experiments, and the nerves were usually stimulated near the stellate ganglion; it is very improbable therefore that death was due to an escape of current to the heart: it probably was due simply to the inability of the heart in its weakened and exhausted condition to respond to the demands made upon it by the stimulation of the accelerators.

RELATION OF THE VAGI TO THE ACCELERATORS; PROTECTIVE ACTION OF THE VAGI UPON THE HEART.

Stimulation of the vagus after section of the accelerators. — In my previous paper I have called attention to two effects of the section of the accelerators upon the results of stimulating the vagi; (1) the

same stimulus applied to the vagus causes a greater slowing of the heart after the accelerators are cut, than before, and (2) the "escape" of the heart during a long continued stimulation of the vagus is less complete after the accelerators are cut.

Other effects of the section of the accelerators in relation to the stimulation of the vagus will be described later in this paper; one other point may be mentioned here although I have but few experiments to quote. A number of physiologists¹ state that while stimulation of the accelerators causes a shortening of both systole and diastole, stimulation of the vagus causes a prolongation of diastole and as a rule but little effect upon the duration of systole. In comparing the effects of stimulating the vagus in different experiments of my own I often have observed that in those cases in which the accelerators were intact and in tonic activity stimulation of the vagus had little effect upon the duration of the systole, while in those in which the accelerators had been cut a very considerable prolongation of systole frequently occurred. Thus in experiment C (see p. 402) after the accelerators were cut stimulation of the vagus caused the systole to be prolonged from 0.26 to 0.345 seconds or over 32 per cent.

Stimulation of the accelerators after section of the vagi. — The tonic activity of the vagi limits the effect of stimulating the accelerators; this is shown in two ways. In the first place stimulation of the accelerators with sub-maximal stimuli has a greater effect upon the heart after than before section of the vagi if these are in tonic activity. Thus in one experiment stimulation of the accelerators with a weak current caused the heart rate to increase from 16 to 24 beats in 10 seconds when the vagi were intact; section of the vagi caused the heart rate to increase to $26\frac{1}{2}$; stimulation of the accelerators with the same strength of current as before caused the heart rate to increase to 34 in 10 seconds. With very strong stimuli, however, the acceleration is the same before and after section of the vagi, for now the effect of the vagi is completely overcome and the heart is accelerated to its maximum rate.

In the second place, the after-effect of stimulation of the accelerators is much more marked after section of the vagi; the heart returns more slowly to the previous rate. The following experiment illustrates this point.

¹ Cf. HÜRTLE: *Archiv f. d. ges. Physiol.*, 1891, xlix, pp. 86-88.

Experiment M. Large dog. Morphine and ether. Curare. Accelerators cut.

Time. Hrs. min. sec.	Heart-beats in 10 seconds.	Time. Hrs. min. sec.	Heart-beats in 10 seconds.
1 51	20—		
	R. annulus stimulated for 10 seconds; coil 10 cm.		R. annulus stimulated for 10 seconds; coil 10 cm.
	22½		24
	23½+	1 58	28
30	19½+		26½
55	R. vagus cut.		23
57 30	21+	30	21+
			20½
			20

Antagonism of the accelerator and inhibitory nerves in their effects upon the duration of systole and diastole. — I have shown elsewhere that, contrary to the view of Baxt, when the accelerators and vagi are stimulated simultaneously, the effect upon the heart rate is determined by the relative strength of the two stimulating currents, and that for sub-maximal stimuli the result is approximately the arithmetical mean of the effects of stimulating the nerves separately.¹ Does this law of the antagonism of these nerves hold good for both systole and diastole? My experiments, which however have not been very numerous upon this point, indicate that this is the case. In such experiments as these it is necessary to use currents the strength of which can properly be compared with each other as regards their effect upon the heart; for while a relatively weak stimulation of the accelerators will cause a shortening of the systole, a stronger stimulation of the vagus is required to prolong this phase of the heart's contraction, and on the other hand a stimulus which, when applied to the vagus, will cause a very great prolongation of diastole may, when applied to the accelerators, affect neither systole nor diastole. In order to cause a prolongation of the systole by stimulating the vagus, it is sometimes necessary to use a current strong enough to bring the heart to a standstill; then, as the heart escapes from this standstill, the systoles are found to be prolonged.

If we accept a suggestion that has been made,² namely, that those

¹ HUNT: Journal of experimental medicine, 1897, ii, p. 171. These results have since been confirmed by v. Cyon (Archiv f. d. ges. Physiol, 1898, lxx, p. 244), Wertheimer (Journal of physiology, 1899, xxiii, supplement, p. 20), and at least the essential part of them by Frank (Sitz.-Ber. d. Ges. f. Morphol. u. Physiol., Munich, 1897, i), quoted from the Jahres-Ber. d. Physiol., 1898, vi, p. 64.

² HÜRTLE: Archiv f. d. ges. Physiol., 1891, xlix, p. 89.

nerve fibres which affect systole are different physiologically from those which affect diastole, the differences noted above may be explained by supposing that one set of fibres is much more irritable to electrical stimulation than the other.

Whatever the explanation, it is undoubtedly a fact that at times when the accelerators and vagi are stimulated simultaneously the systole may be shortened as greatly as when the accelerators are stimulated alone, while the duration of diastole may be either unchanged or even slightly prolonged.¹ Such results as these do not prove, however, that these nerves are not purely antagonistic; they only show that when the effects upon the different phases of the cardiac cycle are considered, the strength of the currents were not comparable, and that in order to bring out the true relations it is necessary to consider the phases separately. If the accelerator and inhibitory nerves are stimulated with currents which when applied separately to the nerves cause changes in one or other of the phases which are comparable (*i. e.* neither stimulus must be a super-maximal one), the result is almost the exact arithmetical mean of the effect produced when the nerves are stimulated separately.

It is very easy to pass the limits of strengths of current which are comparable, and then the accelerator or inhibitory influence will preponderate in the one or the other phase, just as it does when the entire cardiac cycle is considered and one set of fibres is stimulated with a relatively much stronger current than the other.

The above considerations explain the cases in which one nerve gains the mastery in the one or the other phases of the heart's action.

The table on page 426, from one of my experiments, illustrates these points, and shows how perfect the antagonism of the accelerator and inhibitory nerves may be if care is taken to select stimuli of proper strength.

Thus when the two nerves were stimulated together the influence of the accelerators predominated during systole and that of the vagus during diastole, but in each case the effect of the one nerve was diminished by that of the other.

Mutual antagonism of the inhibitory and accelerator nerves in virtue of their tonic activity. — Since both the inhibitory and accelerator

¹ Frank (*loc. cit.*) obtained similar results, but seems (I have not seen the original paper) to have interpreted them as indicating that the antagonism of the accelerators and inhibitory fibres is not perfect when their effect upon systole is considered.

	Duration of Systole.	Duration of Diastole.		Per cent.
Before stimulation	0.25"	0.37"		
Vagus stimulated alone . .	0.27"	0.61"	{ Systole prolonged . Diastole prolonged	8 65
Accelerators stimulated alone	0.18"	0.30"	{ Systole shortened . Diastole shortened	28 19
Both nerves stimulated . .	0.22"	0.45"	{ Systole shortened . Diastole prolonged	12 21

nerves are usually in tonic activity and are also antagonistic, it would seem to follow necessarily that the tonic activity of the one would limit the tonic activity of the other, so that the heart rate at any time (so far as it depends upon the cardiac nerves) is determined by the relative strength and number of the impulses reaching the heart from the central nervous system. In order to test this supposition it is desirable to determine the heart rate (1) when both nerves are intact and in tonic activity, (2) when the heart is under the influence of the accelerators alone, (3) when it is under the influence of the inhibitory nerves alone, and (4) when both nerves are divided. Such an experiment can be performed by suspending the activity of one of the nerves in such a manner that it can readily be restored again; this may easily be done by cooling the vagus. When the dog's vagus is cooled to about 0° C., the power of the inhibitory fibres to conduct impulses is lost,¹ but it can readily be restored by warming the nerve; this method was employed in a number of experiments, of which the following is an example.

Experiment 153. Small bitch. Morphine and ether. Curare. Stellate ganglia carefully exposed. Vagi cooled by passing cold alcohol through metal tubes upon which the nerves lay.

Time. Hrs. min.	Heart-beats in 10 seconds.	Time. Hrs. min.	Heart-beats in 10 seconds.
10 45	17+	11 5	16½
	Vagi cooled.	12	Vagi cooled.
48	25	16	19+
53	29+	17	20
	Vagi warmed.		Vagi cut.
55	16	18	20½
	Accelerators cut.		

¹ HOWELL, BUDGETT, and LEONARD: *Journal of physiology*, 1894, xvi, p. 304.

These results may be expressed in the following tabular form : —

Under the influence of both nerves the heart rate was	17+
Under the influence of the accelerator nerves the heart rate was	29+
Under the influence of the inhibitory nerves the heart rate was	16
After section of both nerves the heart rate was	20½

This experiment shows very clearly that the acceleration following section of the vagi is due in part to the tonic activity of the accelerators, but it shows also that it is not due entirely to this factor, for section of the vagi still caused some increase in the heart rate after section of the accelerators.

It follows from such experiments as the above that the extent of the acceleration following section of the vagi is determined not only by the condition of the cardio-inhibitory centre, but also by that of the accelerator centre. If the tonic activity of the accelerator centre is very great and that of the cardio-inhibitory centre small, section of the vagi will lead to but little increase in the heart rate. In the exceptional cases in which the accelerators are not in activity, the increase of the heart rate following section of the vagi is determined solely by the condition of the cardio-inhibitory centre. In some experiments the entire tonus of the inhibitory nerves seemed to be exerted in holding the accelerators in check; for while cooling of the vagi caused an acceleration of the heart when the accelerators were intact, after section of the latter nerves neither cooling nor section of the vagi caused any change in the heart rate.

In a similar manner the extent of the slowing of the heart following section of the accelerator nerves is determined not only by the condition of the accelerator centres, but also by that of the cardio-inhibitory centre.

That the normal heart rate is determined by the tonic activity of the cardiac nerves, can scarcely be doubted;¹ the varying effect of cutting all the nerves is strong evidence for this view. Thus after section of both the accelerator and inhibitory nerves one of three conditions results: (1) the heart rate is faster, (2) the heart rate is slower, or (3) the heart rate is the same as before the nerves were divided. Which of these three conditions results is determined by the relative strength of the impulses reaching the heart through the cardiac nerves. If the inhibitory impulses are the stronger, section of all the cardiac nerves causes the heart to beat more

¹ Cf. v. CYON: *Archiv f. d. ges. Physiol.*, 1898, lxx, p. 242.

rapidly; if the accelerator impulses are the stronger, section of the nerves causes the heart rate to become slower.

In many of the experiments described above it is evident that the vagi restrained the activity of the accelerators;¹ and so, since fatigue and decrease in the irritability of the heart result from the action of the latter nerves, the vagi acted as a protection to the heart.

Moreover, there is evidence that, so far as the condition of the heart can be judged by its rate, stimulation of the vagus has a beneficial influence upon the mammalian heart, as Gaskell showed it to have in cold-blooded animals. Thus if the accelerators be intact and the peripheral end of one vagus (both vagi having been divided) be stimulated a number of times with currents of moderate intensity, the heart rate is frequently greater after than before the vagus was stimulated. This increase in the heart rate is not to be confounded with the acceleration which sometimes follows immediately after stimulation of the vagus, and which is due to the accelerator nerve fibres present in the vagus or vago-sympathetic trunk; the former is of much longer duration than the latter, and seems to be due to an improvement in the condition of the heart, as a result of which the impulses reaching this organ through the accelerator nerves become more effective. This effect of stimulating the vagus was well shown in an experiment upon a dog: the heart rate some time after section of the vagi was 33 in 10 seconds; the peripheral end of one vagus was stimulated with a weak, slowly interrupted induced current for 25 minutes, short intervals of rest alternating with longer periods of stimulation; after the stimulation the heart rate was 42 in 10 seconds, and it continued at this rate for some time. Such changes in the rate did not occur during periods of rest of equal duration.

Another illustration of the protective influence of the vagus over the heart is found in some experiments in which the vagus and accelerators were stimulated simultaneously for some time. Attention was called above to the fact that when the accelerators were

¹ In a similar manner the tonic activity of the accelerators checks the action of the vagi; if the latter are thrown into activity reflexly, or if the nerves be stimulated directly, the effect upon the heart is less when the accelerators are intact; thus the accelerators prevent excessive action of the vagi, and so a long continued lowering of the blood pressure which might be injurious to the functions of some of the organs. Of course, if the stimulation of the vagi is excessive, as in asphyxia, for example, the effect of the accelerators may be entirely overcome, just as the effect of the tonic activity of the vagi may be entirely overcome by a powerful stimulation of the accelerators.

thus stimulated it happened frequently that after the stimulation the rate of beat was considerably less than it was before the stimulation, and this was considered to be due to fatigue in the heart. If, however, the vagus was stimulated at the same time as the accelerators, the decrease in the rate after the stimulation ceased was, as a rule, much less, or did not occur at all. In other experiments, instead of stimulating the two nerves simultaneously the effect of stimulating the accelerators after a period of rest was compared with the effect of stimulating them after an equally long period of stimulation of the vagus; not only was the maximum acceleration greater in the latter case, but it was of much longer duration. It should be added that in order to obtain this result the stimulation of the accelerators must follow that of the vagus immediately; if a short interval, even one of a few minutes, elapsed between the two stimulations, the result was the same as when the accelerators were stimulated after a period of rest.

Finally, in most of the experiments in which death resulted from stimulation of the accelerators the vagi had been divided.¹

PART II.

REFLEX ACCELERATION OF THE HEART.

The cause of reflex acceleration.—Many text-books of physiology allude to the possibility of reflex acceleration of the heart being produced in two ways: (1) by diminution of the tonus of the vagus, and (2) by stimulation of the accelerator centres. Very few of those who have studied this subject, however, speak of the former possibility; usually all cases of reflex acceleration are referred to stimula-

¹ Death of the heart also resulted sometimes from the intravenous injection of hot normal saline solution or of Ringer solution, and it seemed to occur much more frequently in those animals in which the vagi had been divided. One experiment of this kind was especially interesting. Before the vagi were divided a considerable quantity of normal saline solution was slowly injected into the femoral vein from a fountain syringe; the temperature of the solution in the syringe was 53° C., but it was probably several degrees colder when it entered the vein. The injection increased the rate of beat, but not markedly (from 26½ to 34½ beats in 10 seconds), and no bad effects were produced; on the contrary, the condition of the circulation seemed to be decidedly improved. The vagi were divided, and some time afterwards a much smaller amount of the same solution was injected. The temperature of the liquid in the syringe was now but 50° C.; the heart-beats, however, were increased to 47 in 10 seconds; soon they could not be counted; the blood pressure fell and the dog died.

tion of the accelerator nerve. This attitude is well illustrated by two of the most elaborate articles dealing with the innervation of the mammalian heart which have appeared within recent years — that of Roy and Adami,¹ and of v. Cyon.²

Roy and Adami describe reflex acceleration resulting from the stimulating of sensory nerves, and attribute it to a stimulation of the accelerator nerves; in fact, when studying the effect of these nerves upon the heart, these authors stimulated, as a rule, a sensory nerve instead of the accelerators directly, as they considered the reflex acceleration obtained in this manner to be equivalent to the effect of stimulating the nerves themselves.

Von Cyon describes reflex acceleration following the stimulation of a number of afferent nerves, and seems to ascribe it in all cases to a stimulation of the accelerators. Thus stimulation of a third root of the depressor,³ which he has found in certain animals of different species, causes a reflex acceleration, and v. Cyon thinks that this shows that the nerve fibres of this root are connected in a special manner with the accelerator centre. It is worthy of note, however, that v. Cyon emphasizes the fact that in these experiments the vagi were intact, and in at least one experiment the vagus centre seemed to be in a condition of exaggerated activity as a result of the morphine used as an anæsthetic; hence there is no evidence that in these experiments the reflex acceleration was not due to a diminution of the tonic activity of the vagi. Von Cyon also describes an experiment in which stimulation of the central end of the superior laryngeal caused reflex acceleration;⁴ but here also the vagi were intact and in tonic activity, as their subsequent section showed. Moreover, the increase in the heart rate from stimulating the superior laryngeal was far less than that following division of the vagi.

Careful examination of the accounts of various other experiments on this subject shows that in most of the cases in which reflex acceleration has been described the vagi were intact, and there is frequently

¹ ROY and ADAMI: *Philosophical transactions*, 1892, 183 B, p. 254.

² VON CYON: *Archiv f. d. ges. Physiol.*, 1898, lxx, p. 126.

³ This "third root" of the depressor springs from the superior cervical ganglion or from the cervical sympathetic. I may mention in this connection that Dr. Harrington and I found a small nerve in a calf lying very near the vagus and ending in the superior cervical ganglion: stimulation of this nerve caused a marked fall of blood pressure and a slight slowing of the heart. Thus this nerve corresponded, physiologically, to the depressor.

⁴ VON CYON: *op. cit.*, p. 149, Table III.

evidence to show that they were in a condition of tonic activity. In the description of other experiments nothing is said as to whether the vagi were intact or not, while in a few the statement is made that reflex acceleration occurred after division of the vagi. Almost every statement of the latter kind with which I am acquainted is, however, open to criticism. Thus in some of the older experiments not only was the acceleration very slight, but it was accompanied in many instances by changes in the blood pressure sufficiently great to account for the changes in the heart rate.

Reflex acceleration has been described as resulting from stimulation of the depressor after section of the vagi; Bayliss,¹ for example, describes such an experiment, and reproduces a tracing showing the acceleration. An examination of this tracing shows that the acceleration is very different from that observed when the accelerators are stimulated directly, and arouses the suspicion that it is not a case of true reflex acceleration at all. When the accelerator nerves are stimulated directly, there is a long latent period, and the acceleration is developed slowly; after the stimulation ceases the heart returns slowly to its previous rate. In this tracing the heart rate remained unchanged during the first two or three seconds of stimulation; then it suddenly doubled, and the heart continued at this greater rate until after the stimulation had ended, when it suddenly returned to its previous rate, *i. e.* to just one half the accelerated rate. An examination of the heart in such cases as the above, in which the rate is slowed suddenly to one half the previous rate, usually shows that this is due to the failure of the ventricles to follow one half of the auricular beats; when, on the contrary, the heart rate is suddenly doubled, the ventricles are found to be responding to all of the auricular beats. In many animals this lack of co-ordination in the beats of the auricles and ventricles is made to disappear by influences causing slight changes in the blood pressure or respiration, by movements of the animal, by slightly pulling the vagi, etc., and it is possible that some such changes as these were the cause of the acceleration in Bayliss's experiment. On the other hand it must be remembered that stimulation of the accelerators increases the ease with which impulses are conducted from auricle to ventricle, and it is possible that in the above experiment the doubling of the heart rate was after all due to a reflex stimulation of the accelerators acting in this manner; still, I know of no experiments in which direct stim-

¹ BAYLISS: *Journal of physiology*, 1893, xiv, p. 313.

ulation of the accelerators produced this effect without at the same time causing an increase in the rate of the entire heart.

An experiment by Barbèra very similar to the one described by Bayliss is brought forward by v. Cyon¹ as evidence that reflex acceleration may under some circumstances be produced by stimulation of the central end of the cervical sympathetic. In this experiment, in which the vagi had been cut, the injection of a solution of sodium phosphate had caused a decrease of the heart rate to one half the previous rate; stimulation of the cervical sympathetic, as is shown by the curve published, caused the heart rate to increase from 10 to 20 beats in 5 seconds; ² the latter was practically the rate at which the heart was beating before the injection of sodium phosphate. Apparently the heart continued to beat at this rate for some time after the stimulation ended. Evidently this experiment is open to the same criticism as the one discussed above, and it hardly can be regarded as a satisfactory case of true reflex acceleration.

Barbèra³ describes the effect of stimulating the depressor after section of the vagi in the experiment cited by Cyon, just mentioned. He does not publish the curve, or give many details of the stimulation, but merely states that the heart rate increased as a result of stimulating the depressor from 240 to about 270 beats per minute, while the blood pressure fell from 103 to 86 mm. This may be a case of true reflex acceleration; but it may fairly be asked if in an animal in which, apparently as a result of repeated injections of sodium phosphate, the heart rate was as easily affected, as numerous statements show it to have been in this one, the fall of blood pressure may not have been the cause of this acceleration of the heart. I may add, moreover, that I know of no experiment in which the evidence for the occurrence of reflex acceleration after section of the vagi is stronger than in this one.

Attention was called above to the fact that very few of the authors who speak of reflex acceleration take into consideration the possibility of its being caused by diminution of the tonus of the vagi; in fact I know of but one paper (by MacWilliam) dealing directly with

¹ VON CYON: *op. cit.*, pp. 202-203.

² It may be that in some of these cases the doubling of the rate of the ventricle was only apparent, one strong beat being followed by a weaker beat; the result being that the two beats were recorded by the mercury manometer as one. However these changes are produced, they are evidently not satisfactory evidence of a reflex stimulation of the accelerators.

³ BARBÈRA: *Archiv f. d. ges. Physiol.*, 1897, lxxiii, p. 444.

this subject. Before speaking of MacWilliam's work a few words may be said about some experiments of other physiologists bearing upon this question.

Schmiedeberg,¹ in his classical paper on the accelerator nerves of the dog, describes two experiments in which reflex acceleration was obtained by stimulating the central end of one of the limbs of the annulus of Vieussens. Schmiedeberg does not state whether the vagi were cut or not, but I infer that they were not, and from the fact that the heart rate increased later in the experiment I infer that they were in a condition of tonic activity. Schmiedeberg calls attention to the fact that in one of these two experiments the course of the acceleration was different from that resulting from direct stimulation of the accelerators, in that the after-effect was very short, and he expresses a doubt as to whether the acceleration was due to a reflex stimulation of the accelerator nerves; he does not suggest, however, that it may have been due to a diminution of the vagus tonicity.

Asp² made a number of experiments on the effect upon the heart rate of stimulating sensory nerves both before and after section of the vagi; he also made four experiments in which the accelerators were cut. Asp observed slight acceleration upon stimulating sensory nerves after the vagi were cut; the effect upon the blood pressure was variable. In two of the four experiments in which the accelerator nerves had been cut slight reflex acceleration occurred; in the two other it did not occur, although it had been obtained in all four experiments before the accelerators were cut. Asp was endeavoring to determine whether reflex acceleration is due to a stimulation of the accelerator nerves or, as he puts it, to "a constriction of the arteries of the brain, caused by a stimulation of the sensory nerve, by which the pressure on the vagus centres was reduced and the heart became more rapid." Neither Asp nor Schmiedeberg seems to have considered the possibility of the reflex inhibition of the cardio-inhibitory centre.

These experiments of Asp are sometimes cited as evidence of reflex stimulation of the accelerator nerves, and Asp himself was inclined to interpret them in this manner, although he states distinctly that he did not consider the question closed. The reflex acceleration was not marked; blood pressure changes could not be

¹ SCHMIEDEBERG: Sitz.-Ber. d. sächs. Gesell. d. Wiss., math.-phys. Cl., 1871, p. 152.

² ASP: Sitz.-Ber. d. sächs. Gesell. d. Wiss., math.-phys. Cl., 1867, p. 188.

excluded, and finally, as Asp points out, the heart was irregular and the effect of stimulating sensory nerves very uncertain.

Knoll¹ found that compression of the heart, either by the finger or by inflating the pericardium with air, caused an acceleration of the heart, and he showed that this acceleration was due to a diminution of the tonicity of the vagi.

MacWilliam² is apparently the only author who has given careful attention to the question as to the manner in which reflex acceleration is brought about when an ordinary sensory nerve is stimulated, but he has published only a preliminary paper containing few details. MacWilliam compared the latent period of direct and of reflex acceleration, and reached the conclusion that the latent period of the latter is too short for the acceleration to be referred to a stimulation of the accelerator nerves; he thinks it is due to a diminution of the tonus of the vagi. The effect upon the heart rate of stimulating the sensory nerves before and after section of the vagi, and of stimulating the accelerators, was also studied by MacWilliam, with the result that reflex acceleration was obtained after the accelerators were cut if the vagi were intact, but not after the vagi were cut, although the accelerators were intact. From these experiments MacWilliam drew the conclusion that, ordinarily, reflex acceleration is due to a diminution of the tonus of the vagi.

The afferent nerves by which reflex acceleration is produced. — The nature of the afferent nerve fibres by which reflex acceleration and reflex slowing of the heart are produced has received but little attention. Tigerstedt,³ after discussing the various experiments on this subject, states what may perhaps be regarded as the current view of physiologists, namely, that both the accelerator and inhibitory nerves can be thrown into reflex activity by the stimulation of almost all afferent nerves.

There is evidence, however, that the various sensory nerves differ in their effect upon the heart; some for example cause as a rule reflex acceleration, others, reflex slowing. To the latter class, as Tigerstedt pointed out, belongs the trigeminus; stimulation of this nerve

¹ KNOLL: *Lotos, neue Folge*, 1881, ii, p. 14.

² MACWILLIAM: *Proceedings of the royal society, London*, 1893, liii, p. 464. It is but fair to myself to state that most of my experiments were performed before I learned of MacWilliam's paper; in fact, the greater part of this section of my paper was written a number of years ago, and originally included in a thesis presented to the Johns Hopkins University for the degree of doctor of philosophy.

³ TIGERSTEDT: *Lehrbuch der Physiologie des Kreislaufes*, 1893, p. 289.

seems always to cause reflex slowing, if it has any effect at all upon the heart. Asp¹ states that, as a rule, he observed acceleration to follow stimulation of the central end of muscular branches of nerves; but in some experiments reflex slowing occurred. Tengwell,² however, found the stimulation of muscular nerves had but little effect upon the heart rate. Roy and Adami³ found reflex acceleration usually resulted from stimulation of the sciatic nerve; sometimes the acceleration was followed by a slowing of the heart. The latter nearly always occurred when the splanchnic nerve was stimulated. Schmiedeberg⁴ observed in two of his experiments that stimulation of the central end of one limb of the annulus of Vieussens caused reflex acceleration, whereas stimulation of the other limb caused reflex slowing; he suggests that there are several varieties of afferent nerve fibres, some of which cause reflex acceleration and some reflex slowing.

Statements and speculations as to the nature of the afferent nerve fibres concerned in reflex acceleration, however, have only a secondary interest, so long as the question of the manner in which this acceleration is caused is left undecided; for if it should be shown that reflex acceleration is in reality due to an inhibition of the cardio-inhibitory centre, the effect of stimulating various nerves might be determined solely by the condition of this centre at the time of stimulation.

ON THE MANNER IN WHICH REFLEX ACCELERATION IS PRODUCED.

The problem whether the reflex acceleration resulting from the stimulation of sensory nerves is caused by a diminution of the tonicity of the vagi, or by an increased action of the accelerators, was approached from three standpoints: (1) the details of some of the

¹ ASP: *op. cit.*, p. 183. The statement of Asp that mechanical stimulation of the sciatic plexus causes a reflex slowing of the heart, whereas electrical stimulation causes an acceleration, is often quoted. I can find but one experiment of this kind described in Asp's paper (p. 182), and this is most unsatisfactory on account of the great differences produced in the blood pressure in the two cases; with mechanical stimulation the blood pressure rose 106 mm., while with electrical stimulation there was a rise of but 37 mm. Some of Asp's experiments upon the effect of stimulating the lumbar cord are open to a similar criticism; thus he compares the effects of two stimuli (one mechanical and the other electrical) upon the heart rate, although in the one case the blood pressure rose to 100 mm. and in the other to 174 mm. Some of these experiments will be referred to again.

² TENGWELL: *Skandinavisches Archiv f. Physiol.*, 1895, vi, p. 230.

³ ROY and ADAMI: *Philosophical transactions*, 1892, 183 B, p. 258.

⁴ SCHMIEDEBERG: *Ber. d. sächs. Gesell. d. Wiss., math.-phys. Cl.*, 1870, p. 152.

events occurring in the heart when it was thrown into a condition of acceleration in various ways were investigated, (2) the accelerators were cut and sensory nerves stimulated, and (3) the vagi were divided and sensory nerves stimulated.

The duration of systole and diastole and the latent period when the heart rate is increased in various ways.—The duration of systole and diastole, and the latent period of acceleration, were determined when the heart rate was increased by the stimulation of a sensory nerve, and these results were compared with those obtained by cutting the vagi and by stimulating the accelerators directly. If the acceleration occurring in the former case is due to a diminution of the tonic activity of the vagi, we should expect to find the course of the acceleration similar to that resulting from section of the vagi, rather than to that observed when the accelerators are stimulated directly; the former is, as a rule, the case, as the following experiments show.

The duration of systole and diastole, and of the latent period, was determined by means of Hürthle's manometer, in the manner described in the first part of this paper. At times the dicrotic wave on the curve of carotid pressure became so indistinct that it was impossible to determine accurately the duration of systole; such tracings could be used, however, for determining the latent period.

The results obtained from the various experiments were so uniform that only one or two experiments of each class need be described.

Section of the vagi.—The following experiment shows the usual effect upon the heart-beat of cutting the vagi when these are in a condition of tonic activity.

Experiment A. Very small dog. Morphine and ether. Left carotid connected with Hürthle's manometer. Left vagus had been cut.

Time. Hrs. min.	Duration in seconds of		Time. Hrs. min. sec.	Duration in seconds of	
	Systole.	Diastole.		Systole.	Diastole.
3 50	0.175	0.495		0.165—	—
	0.165	0.495	3 50	—	—
R. vagus cut.	0.175	0.365+		0.155+	0.260
	0.165	0.365+		—	0.260
	0.170—	0.330		0.150—	—
	0.165	0.305		0.145	—
	— ¹	—		—	—
	—	0.280+	10	0.140	0.255
	0.165—	—	12	0.130+	0.255
	—	—	14	0.120	0.255

¹ In this and subsequent tables the dash (—) means that the curves were not counted out in full; the labor of counting these tracings to hundredths of seconds is very great.

These results are shown in the plotted curve of Fig. 6 better than in the table; the ordinates represent the duration of systole and

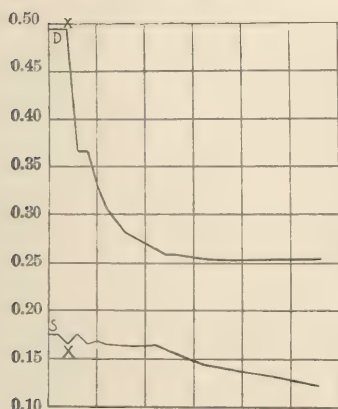


FIGURE 6. Experiment A. Section of right vagus. The ordinates represent the duration of systole, *S*, and of diastole, *D*, in 0.05 seconds; the abscissæ, 5 heart-beats.

the much more slowly developed and relatively less marked effect upon the systole. The shortening of diastole began in the heart-beat during which the vagus was cut, and had reached almost the maximum before the shortening of systole began. These results are in accord with the well-known fact that it is the diastole which is most easily and quickly affected when the heart rate is altered, and that the influence of the vagus upon diastole is greater than its influence upon the systole.

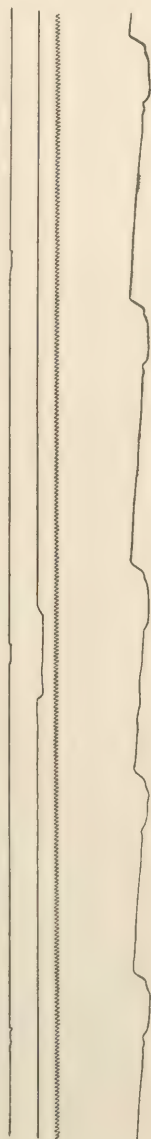
Results very similar to the above are obtained when the heart returns to its normal rate after it has been slowed by stimulation of the peripheral end of the vagus or when it has been slowed reflexly.

Stimulation of the accelerators.—An experiment was described in the first part of this paper (p. 402) showing the effect upon the duration of the systole and diastole of cutting

diastole in 0.05 of a second, the abscissæ five heart-beats. In Fig. 7 a small part of the original tracing is reproduced.

The chief effects upon the heart rate of cutting the vagi, as shown by the above experiment, are (1) the very sudden and great decrease in the duration of diastole, and (2)

FIGURE 7. Two thirds the original size. Experiment A. Part of record taken with Hürthle's manometer to show effect of cutting the right vagus. Time in intervals of 0.01 and 1 second intervals. To be read from left to right.



the accelerator nerves; the following table and curve (Fig. 8) show the effect of stimulating the accelerators in this experiment.

Time.		Duration of		Heart-beats in 10 seconds.
Hrs.	min.	Systole.	Diastole.	
2	3	0.285	0.310	16½
		0.300+	0.325	
R. ann. stim. ; coil 10 cm.				
		0.285	0.305	
		0.265	0.330	
		0.300	0.330	
		0.280	0.305	21½
		0.265	0.265	
		0.240+	0.275	
		0.235	0.260	
		0.215+	0.245	
		—	—	
		0.230	0.240—	
		—	—	
		0.195	0.225	
		—	—	
		0.180	0.220+	
		—	—	
		0.175	0.210+	
		—	—	
		—	—	
		0.160	0.215+	
		0.155	0.200	
Stim. off annulus.				
		0.160	0.190+	(Every 5th beat counted.)
		0.145+	0.205	28+
		0.140+	0.210+	
		0.145+	0.205+	
		0.140	0.220	

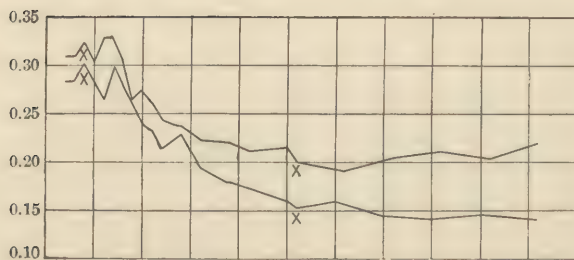


FIGURE 8. Experiment C. Stimulation of the right annulus (x to x). The ordinates represent the duration of systole, S , and of diastole, D , in 0.05 seconds; the abscissæ, 5 heart-beats.

The exceptionally long duration of the systole in this experiment was caused by the section of the accelerators.

This experiment shows that stimulation of the accelerators causes a shortening of systole as

well as of diastole, and that the latent period of each is very long; in fact, the maximum shortening occurred after the cessation of the stimulation.

Curves very similar to the above are obtained when the accelerators are stimulated during a long stimulation of the vagi, by which the heart is slowed. Occasionally, however, when the heart rate is very slow, either in consequence of the stimulation of the vagi,¹ or of the tonic activity of these nerves, or from other causes, and the stimulus applied to the accelerators is very strong, the latent period is much shorter than in the above experiment,² and the diastole is much shortened before the shortening of the systole begins. In such cases the curve is intermediate in form between those resulting from section of the vagi and those usually following stimulation of the accelerators.

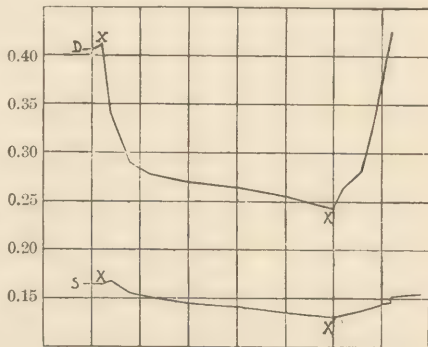


FIGURE 9. Experiment E. Stimulation of saphenous. (See above table.) The ordinates represent the duration of diastole, *D*, and of systole, *S*, in 0.05 seconds; the abscissæ represent 5 heart-beats.

Acceleration of the heart resulting from stimulation of a sensory nerve.—The following experiment illustrates the effect upon the heart rate of stimulating a sensory nerve.

Experiment E. Medium-sized dog. Morphine and ether; curare. The following table and curves (Figs. 9 and 10) show the effect upon the heart of stimulating the saphenous nerve.

¹ François-Franck (*Travaux du laboratoire de Marey*, 1878–79, p. 80) states that the latent period is prolonged when the heart is under the influence of the vagus; I have found just the opposite to be the case. There is, moreover, the following difference: when the vagi have been divided, or when they are not in tonic activity, the latent period of the accelerators is found to be long in both systole and diastole, and the shortening of one does not begin before that of the other. If, however, the vagi are in activity, stimulation of the accelerators may cause a marked shortening of diastole before the duration of systole is at all affected. When, on the other hand, the vagus is stimulated, the diastole is always prolonged before the systole, *i. e.* the latent period of stimulation of the vagus applies especially to the systole.

² Hürthle (*Archiv f. d. ges. Physiol.*, 1891, xlix, p. 89) describes an experiment on a very slowly beating heart in which the second diastole was shortened; I never have observed a shortening of any diastole before the fourth as a result of stimulating the vagus.

Time.		Duration in seconds of		Time.		Duration in seconds of	
Hrs. min.		Systole.	Diastole.	Hrs. min.		Systole.	Diastole.
11	23	0.175	0.415			—	—
		0.175	0.420			—	—
	R. saphenous stimu-					—	—
	lated for 10 secs.;					0.145	0.265
	coil 11 cm.					—	—
		0.180—	0.350			—	—
		—	—			—	—
		0.165	0.300			—	—
		—	—			0.140	0.255
		0.160	0.290		Stimulus off sappe-		
		—	—		nous.		
		—	—			0.140+	0.270+
		—	—			—	—
		0.155+	0.280			0.145+	0.290+
		—	—			—	0.330+
		—	—			0.150+	—
		—	—			0.160	0.430+
		—	—			—	—
		0.150	0.275			—	—
		—	—			0.165	0.505+

Examination of the above table and curves shows that the shortening of the diastole is very marked and the latent period very short; the effect upon the systole is less marked and is more slowly developed. The heart rate also returned very quickly to the normal.

When the effects upon the heart rate of stimulating a sensory nerve are compared with those described above, resulting from cutting the vagi and from stimulating the accelerators, it is very evident that they resemble the former much more closely than they do the latter. When the heart is accelerated by section of the vagi, or by the stimulation of a sensory nerve, the diastole is shortened relatively much more than the systole, and the latent period is very short. When, however, the accelerators are stimulated directly, the systole as well as the diastole is much shortened, and the latent period is very long. Moreover, the after-effect upon the heart rate of stimulating the accelerators directly is often very different from that occurring in reflex acceleration; in the former case the heart continues beating at a rapid rate for some time, whereas in the latter it often returns very quickly to its previous rate or is slowed.

As the results described above are by no means exceptional, but are the rule, I think they can be regarded as strong evidence for the view that in reflex acceleration of the heart diminution of the tonic activity of the vagi plays the chief rôle.

These results are of a special interest, since they suggest that under certain circumstances the cause of any sudden increase in the heart rate, *i. e.* as to whether the increase is due to stimulation of the accelerators or to a diminution of the tonic activity of the vagi, can be determined from the cardiogram of the intact animal or of man.

While in most cases the curves of direct and of reflex acceleration differ in the manner described above, there are exceptional cases in which the difference is not well marked. In some cases of reflex acceleration, for example, the latent period is comparatively long; this occurs most frequently when the heart rate is already rapid and the acceleration relatively small. On the other hand, the latent period when the accelerators are stimulated may be very short; as already described, this occurs when the heart is beating very slowly. Further, the difference mentioned above in the effect upon systole and diastole, in the two cases, is not always marked. Even in these exceptional cases, however, the subsequent course of acceleration usually differs; the maximum shortening is reached much more quickly in reflex than in direct acceleration.

Reflex acceleration after section of the accelerators. — Such an experiment as the following shows that marked reflex acceleration of the heart may occur after the principal nerves containing accelerator fibres have been divided.

FIGURE 10. One half the original size. Experiment E. Part of record taken with the Hürthle manometer to show effect of stimulating saphenous nerve; secondary coil 7 cm. Time in 0.01 and 1.0 second intervals. To be read from left to right.



Experiment 139. Small dog. Morphine and ether. Stellate ganglia and their branches exposed. Blood pressure from left femoral artery.

Time. Hrs. min.	Heart-beats in 10 seconds.	Time. Hrs. min.	Heart-beats in 10 seconds
1 8	14—		—
R. saphenous stim. for 10 sec.; coil 10 cm.	22—	40½	10½
	13½	R. saphenous stim. for 10 sec.; coil 14.	10½
	12+		18½
	11½+		10½ -
{ 1 30 to 1 34	Accel. nerves cut.		10
1 39	14½		9½+
R. saphenous stim. for 10 sec.; coil 10 cm.	19½	51	10½
	11½	R. saphenous stim. for 10 sec.; coil 16 cm.	11
	10		17+
			11½
			10½

Section of the vagi caused the heart rate to increase to 26 beats in 10 seconds.

The accompanying curve (Fig. 11) shows the effect upon the heart rate of one stimulation of the saphenous nerve in the above experi-

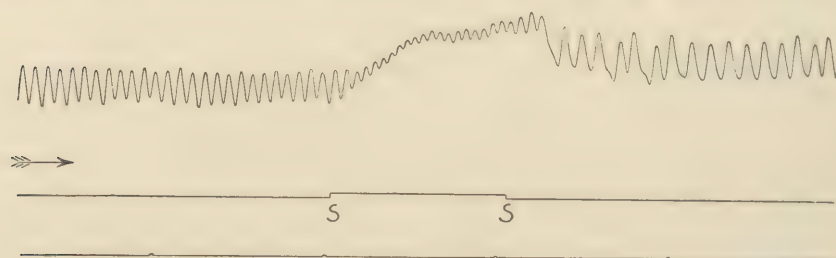


FIGURE 11. Two fifths the original size. Experiment 139. Acceleration of the heart resulting from stimulation of the saphenous nerve, S-S, after section of the accelerator nerves. Time in intervals of 10 seconds. Tracing to be read from left to right.

ment after the accelerators were cut. A glance at this curve shows it to be very different from those obtained when the accelerators are stimulated directly; in the latter case the latent period is much longer, the maximum acceleration is much more slowly reached, and the heart rate returns much more slowly to its previous rate. The reflex acceleration in this experiment was slightly greater before than after the accelerators were cut; this feature, which frequently

occurs, will be discussed below, but it evidently does not interfere in the least with the conclusion that in reflex acceleration diminution of the tonicity of the vagi plays the chief rôle.

Results similar to the above were secured in a large number of experiments. In fact whenever reflex acceleration was obtained with the accelerators intact, it was obtained also after these nerves had been divided, provided the tonicity of the vagus centre was not destroyed by the operation. The operation necessary to expose the accelerators and the section of these nerves tend to reduce or to abolish permanently the vagus tonicity; if this occurs, no reflex acceleration takes place.¹ In order to get the best results it is well to proceed as in the above experiment; the stellate ganglia should be exposed with as little operating as possible, and then some time allowed for the animal to recover. The temperature is prevented from falling by keeping the animal on a zinc box filled with warm water, and the wounds are carefully covered with towels wet with warm saline solution. Finally the nerves are cut with a pair of very sharp scissors, and pulling or crushing of the nerves carefully avoided. All cases in which reflex acceleration occurred before but not after section of the accelerators could be explained by the loss of vagus tonicity resulting from the operation. On the other hand, I had never observed reflex acceleration to occur except when there was clear evidence that the vagi were in tonic activity.²

Another point of interest in this connection (and the one which first led me to suspect that reflex acceleration is due to a diminution of the vagus tonicity) is that the rate reached by the heart during reflex acceleration is never greater than that following the section of the vagi; it may reach this rate, but never exceeds it.

Certain objections may be raised to the conclusion that in such experiments as the above the acceleration was due to a reflex diminution of the tonic activity of the vagi. Thus the acceleration might be attributed to the rise of blood pressure which so often occurs at the same time. It is not at all uncommon, especially when

¹ It is not improbable that the absence of reflex acceleration in the two experiments of Asp referred to above (p. 433), in which the stellate and inferior cervical ganglia had been removed, was due to the loss of tonicity of the vagi resulting from the operation.

² Reflex acceleration also occurs in animals in which subsequent section and stimulation of the accelerator nerves show them to have been in a condition of maximum acceleration; the reflex acceleration in such cases is obviously due to an inhibition of the vagus centre.

the heart is beating very slowly, for stimulation of a sensory nerve to cause a rise of blood pressure and a considerable acceleration of the heart even after all the cardiac nerves are divided;¹ the same result may follow stimulation of the peripheral end of the splanchnic, both when the cardiac nerves are intact and when they have been divided. The course of the acceleration occurring in such cases as these, however, is very different from that which occurs when a sensory nerve is stimulated and the vagi are intact. In the latter case the acceleration begins with considerable suddenness; the second or third beat may be shortened and a very distinct acceleration occur before the blood pressure has begun to rise; in the former case the acceleration begins very slowly; I have never observed it to begin until after the nerve had been stimulated for at least 10 seconds, and the blood pressure had risen very considerably.

Moreover, reflex acceleration frequently takes place when the change in the blood pressure is insignificant.

Another possible cause of the acceleration occurring after the stellate ganglia and their branches have been extirpated remains to be considered, viz. a reflex stimulation of accelerator fibres which pass to the heart in the vagus or vago-sympathetic trunk. As is well known, the slowing of the heart caused by stimulation of the peripheral end of the vagus or of the vago-sympathetic in the dog is sometimes followed by an acceleration; if atropine has been given, acceleration alone may result. This acceleration at present is usually explained by supposing that there are certain accelerator fibres which reach the heart by this route, and the possibility of reflex acceleration being produced by means of such fibres must be considered. Certain considerations, however, make it very improbable that these fibres play any important part in the production of reflex acceleration. In the first place, it is rather exceptional to find any evidence for the existence of accelerator fibres in the vago-sympathetic of the dog; reflex acceleration is very frequently obtained after removal of the stellate ganglia in animals in which no acceleration is observed when the vago-sympathetics are stimulated either before or after the administration of atropine. When stimulation of the vagus does cause acceleration after atropine, the curve closely resembles that observed when the other accelerators are stimulated, and is not at

¹ The acceleration observed in such cases may not be due to the rise of blood pressure, but to the warm blood which is forced suddenly into the heart from the abdominal viscera. Cf. MARTIN: *Physiological papers*, 1895, p. 18.

all like that obtained in reflex acceleration. Moreover, the acceleration caused by the direct stimulation of these nerves is seldom so great as that which is often obtained reflexly by the stimulation of sensory nerves.

Stimulation of sensory nerves after section of the vagi. — The question, Does reflex acceleration occur after section of the vagi? may now be discussed. It may be said at once that in a large number of experiments stimulation of sensory nerves caused either no acceleration at all after section of the vagi, or the acceleration was so slight that it could be referred probably to changes in blood pressure; in no case was there evidence that the slight acceleration was due to stimulation of the accelerator nerves, for such changes in the heart rate occurred after these nerves as well as the vagi had been cut. No reflex acceleration took place after the vagi had been cut in cases in which all the conditions seemed very favorable, *i. e.* in cases in which marked reflex acceleration had been observed before the vagi were cut, and in which, as subsequent examination showed, the accelerators were not in a condition of maximum activity and were very irritable.

The question may be raised, if after the vagi were cut the heart was not already beating at so rapid a rate that the conditions were not favorable for the occurrence of reflex acceleration, although the accelerator centres may have been irritable. This rapid rate of the heart, however, could not account for the entire absence of reflex acceleration, for the maximum rate to which the heart can be accelerated is independent of the rate at which the heart beats before stimulation,¹ and it is very rare for the heart to be in a condition of maximum acceleration after section of the vagi. Still, if the heart was beating slowly before reflex acceleration occurred, the relative increase would be greater, and hence more striking. Accordingly, in a number of experiments in which the heart rate had increased as a result of cutting the vagi, the peripheral end of one or of both of these nerves was stimulated with a current just sufficient to bring the heart back to the rate at which it was beating before the nerves were cut. Stimulation of sensory nerves in such cases never caused any acceleration, although direct stimulation of the accelerators caused a great increase in the rate.

These experiments are of interest in connection with the work of Roy and Adami. These authors agree with me as to the absence of

¹ BOWDITCH: Ber. d. sächs. Gesell. d. Wiss., math.-naturw. Cl., 1871, p. 266.

reflex acceleration after section of the vagi,¹ but give an entirely different explanation. Roy and Adami explain reflex (and also direct) acceleration of the heart as due to a diminution of the vagus tonus *in the heart* resulting from the action of the accelerator nerves; after section of the vagi, reflex or direct acceleration of the heart is impossible, since there is no vagus tonus in the heart to overcome. If this explanation were correct, it is impossible to see why reflex acceleration does not occur when the effect of the vagi upon the heart has been restored by the artificial stimulation of these nerves.

A few experiments on the effect upon the heart rate of stimulating the cerebral cortex may be referred to here. The suggestion that the accelerator nerves may be thrown into activity by processes originating in the cerebrum is frequently made; hence it seemed possible that stimulation of the cerebral cortex might yield interesting results. Accordingly in a number of experiments upon dogs the motor areas and various parts of the frontal and occipital lobes were stimulated with the faradic current. Acceleration of the heart frequently occurred when the vagi were intact and in tonic activity, but no acceleration was obtained after section of the vagi, either when the heart was beating rapidly, or when it was slowed by stimulating the peripheral end of the vagus.

Influence of the tonic activity of the accelerators upon reflex acceleration. — Although, as has been shown above, reflex acceleration is due to a diminution of the tonus of the vagi, and occurs after the accelerator nerves have been divided, yet these nerves, if they are in a condition of tonic activity, exert a modifying influence upon the course of the acceleration. The extent of the reflex acceleration, like the increase in the heart rate following section of the vagi, is in fact determined by two factors, — the cutting off of the influence of the tonic activity of the vagi, which of itself keeps the heart beating slowly, and the removal of the check to the tonic activity of the accelerators.

This influence of the tonic activity of the accelerators is shown in three ways. In the first place, the rate to which the heart is accelerated is, as a rule, greater when these nerves are intact than when they have been divided. Secondly, the course of the acceleration is, or may be, somewhat different; there may be, to begin with, a very sudden and marked acceleration, due to the inhibition of the tonic inhibitory impulses, and then an acceleration more slowly developed,

¹ ROY and ADAMI: Philosophical transactions, 1892, 183 B, p. 267.

due to the accelerator nerves; whereas after section of the accelerators reflex acceleration usually reaches its maximum very quickly, and is often followed by a partial return to the normal while the stimulation continues. In the third place, the after-effect of the stimulation is often different: when the accelerators are intact, the rate may continue rapid for some time after the stimulation ceases, and only slowly return to the normal, or give way to a secondary slowing. If, however, the accelerators have been divided, the rate after stimulation of a sensory nerve usually returns quickly to the normal, or perhaps more frequently is followed by a reflex slowing.

All three of the above points are illustrated by the curves in Fig. 12; these results were obtained from an experiment upon a dog.

Stimulation of the saphenous in this case, when

both vagi and accelerators were intact, caused the heart rate to increase from $22\frac{1}{2}$ to $31+$ beats in 10 seconds. Section of the accelerators caused the heart rate to decrease to $19\frac{1}{2}$ in 10 seconds; stimulation of the saphenous now with the same strength of current as above caused the heart rate to be increased to but $24\frac{1}{2}$ beats in 10 seconds. Of course the objection may be made that the more rapid rate in the former case (*i. e.* when the heart rate increased to 31) was due in part to a reflex stimulation of the accelerators, and not exclusively to a diminution of the tonic activity of the vagi. That, however, the latter factor alone is sufficient to account for the acceleration is shown by the following fact: before the saphenous nerve was stimulated or the accelerators cut, the conductivity of the vagi was suspended by ether vapor with the result that the heart rate increased to 34 in 10 seconds.

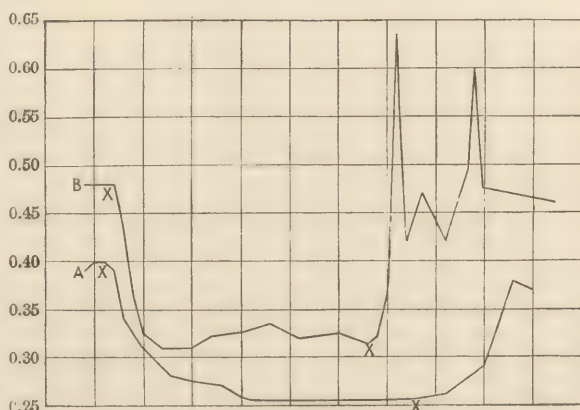


FIGURE 12. Experiment H. Stimulation of the saphenous, A, before, B, after, section of the accelerator nerves. The stimulation continued 10 seconds in each case; the strength of the stimulating current was also the same. Ordinates represent the duration of the heart-beat in 0.05 seconds; the abscissæ, 5 heart-beats.

The rate 31 therefore does not represent the maximum acceleration which might have resulted from inhibition of the inhibitory impulses. The vagi were afterward cut with the result that the heart rate increased to 29 beats in 10 seconds.

To summarize the results of this experiment and to show how completely the heart rate is determined at any given time by the interaction of the inhibitory and accelerator nerves, the following table may be given.

	Heart rate in 10 seconds.
Vagi and accelerators intact and in tonic activity	22
Activity of vagi suspended by ether vapor, the accelerators being intact .	34
Accelerators cut, vagi intact and in tonic activity	19
After section of accelerators and vagi	29
Reflex acceleration, accelerators and vagi being intact	31
Reflex acceleration after section of the accelerators	24
Stimulation of accelerators (weak current), vagi being intact	27
Stimulation of accelerators (current as before), vagi cut	34½

If, returning to the course of reflex acceleration, we compare the two curves given in Fig. 12, the following differences will be observed. When the accelerators were intact and the saphenous nerve stimulated, there was first a sudden marked shortening of the duration of the heart-beat; this was followed by a longer period in which the heart rate was very slowly increased. After cessation of the stimulation the acceleration of the heart continued for some little time. When, on the other hand, the saphenous was stimulated after section of the accelerators, there was also a sudden increase in the heart rate; but this was soon followed by a slight slowing, and immediately after the stimulation there was a very marked slowing.

The curves given above are intended only to illustrate the differences which the section of the accelerators may make in a given experiment in the course of reflex acceleration; they are not intended to serve as types of the reflex acceleration occurring before and after section of the accelerators. No such types can be given, for the course of acceleration is seldom the same in any two experiments. Thus in one experiment the acceleration may be followed by reflex slowing, even during the stimulation of the sensory nerve, although the accelerators are intact and in tonic activity; whereas in another experiment reflex acceleration may continue long after the cessation of the stimulation, although the accelerators have been divided. In any one experiment, however, the section of the accelerators usually

has some such effect as that described in the above case, *i. e.* the maximum acceleration is less and is more quickly developed and there is a greater tendency to a subsequent slowing.

The parts taken by the inhibitory and accelerator nerves in causing reflex changes of the heart rate find a striking analogy in the relation of the oculo-motor and sympathetic nerves in reflex movements of the pupils. Thus, according to Braunstein,¹ reflex dilatation of the pupil is due to an inhibition of the tonic activity of the oculo-motor centre, for it occurs after section of all the pupil-dilating fibres, if the oculo-motors are intact; on the other hand, no reflex dilatation of the pupil occurs after section of the oculo-motors although the pupil-dilating fibres are intact.² Moreover, just as the tonic activity of the accelerator nerves modifies the course of reflex acceleration of the heart, so the tonic activity of the pupil-dilating fibres modifies the course of the reflex dilatation of the pupil; after section of these fibres the dilatation occurs more slowly, as some of the "dilating force" is lost.

Some influences affecting the condition of the cardio-inhibitory centre.—With the exception of the respiratory centre there is perhaps no medullary centre in the cat and dog so easily influenced as that of the inhibitory nerves of the heart; Hering's experiments on rabbits show that this, probably, is true for these animals also.³

No attempt will here be made to discuss the influences affecting the condition of the cardio-inhibitory centre with any degree of fulness; only a few factors will be noted which it is necessary to take into consideration in connection with the question of reflex acceleration.

Some influences increase, others decrease, the tonic activity of the cardio-inhibitory centre; among the former may be mentioned high blood pressure and deficient respiration, and among drugs morphine and, apparently, small doses of curare. Morphine causes slowing of the heart not only by its direct action upon the cardio-inhibitory centre, but also through its action upon the respiration. In animals

¹ BRAUNSTEIN: *Zur Lehre von der Innervation der Pupillenbewegung*, p. 95; Wiesbaden, 1894.

² In man, also, no reflex movements of the pupil are obtained after complete paralysis of the oculo-motor.

The dilatation of the pupil resulting from stimulation of the cerebral cortex is also due, according to Braunstein (p. 116), to a diminution of the tonus of the oculo-motor centre.

³ HERING, H. E.: *Archiv f. d. ges. Physiol.*, 1895, lx, p. 429.

anæsthetized by means of cerebral pressure the vagi are usually found to be in a condition of marked tonic activity.

Ether and large doses of curare, and of chloroform, decrease or abolish the tonus of the vagus centre completely; ¹ operations and loss of blood have the same effect, so that unless great care is taken in operating, the tonus of the vagi is completely lost.

Not only does the extent of the tonus of the vagi vary widely in different animals of the same species, but the susceptibility of the centre to influences which increase or decrease the tonus also varies in different individuals. In most dogs, for example, morphine causes a very slow heart beat, but in some it has almost no effect upon the heart rate, although given in very large doses.

The tonic activity of the vagi seems to be very slight in young animals, and to be very easily abolished in them.

Influence of the condition of the cardio-inhibitory centre upon cardiac reflexes. It is obvious that no inhibition of a centre can occur unless the centre is in a condition of activity; but the question arises, Is a centre more easily inhibited the greater the activity, or is it more easily inhibited when influences are at work which tend, of themselves, to weaken the activity? The results of my experiments upon the cardio-inhibitory centre indicate very clearly that the latter is the case; this was shown best, perhaps, in experiments on dogs narcotized with morphine. In such animals the cardio-inhibitory centre is in a condition of marked activity, and stimulation of a sensory nerve often has at first no effect; if, however, some drug which of itself tends to destroy the tonus of the centre is given, the stimulation of a sensory nerve may cause a marked acceleration of the heart.

Among the drugs which reduce the irritability of the cardio-inhibitory centre are ether and curare, as was mentioned above; if one of these is given to an animal under the influence of morphine, there may be an increase of the heart rate of short duration, and then the slow rate returns; stimulation of a sensory nerve now, however, may easily cause an inhibition of the centre and so an acceleration of the heart. Similar results are obtained in animals anæsthetized by cerebral pressure; in these animals the cardio-inhibitory centre is in a condition of strong activity, and stimulation of sensory

¹ An irregular rhythm of the heart, probably due to the inhibitory nerves, is frequently made to disappear by the administration of ether or of curare, or by the stimulation of a sensory nerve, all of which cause a diminution of the vagus tonus.

nerves may have no effect upon the heart or may cause a slowing. If, however, ether or curare is given, — although no visible change is produced, — stimulation of a sensory nerve usually will cause an inhibition of the centre.

If both vagi are intact and in tonic activity, stimulation of a sensory nerve may have no effect upon the heart rate; but if one vagus be cut, — although this of itself may cause no increase in the heart rate, — stimulation of the same sensory nerve may cause a marked acceleration.

Just the converse of the above holds good for reflex slowing of the heart. If the irritability of the cardio-inhibitory centre has been much reduced so that the heart is beating very rapidly, stimulation of a sensory nerve may have no effect upon it; if, however, the respiration is diminished, or the blood pressure increased in some manner, or intravenous injections of warm normal saline solutions be made, — influences which tend to stimulate the centre, — then stimulation of a sensory nerve may cause a marked slowing of the heart.

Such experiments as those briefly sketched above show that in order to obtain either reflex inhibition or reflex excitation of the cardio-inhibitory centre it is necessary that this centre be in a condition of unstable equilibrium; if the centre is in this condition, the result of stimulating a sensory nerve is determined in part (but only in part, as will be shown later) by the rate at which the heart is beating when the nerve is stimulated: if the heart is beating slowly, reflex acceleration results; if it is beating rapidly, reflex slowing occurs. Thus, in one of many experiments the heart rate was 24 in 10 seconds, and stimulation of the saphenous nerve caused the heart rate to decrease to $17\frac{1}{2}$. A small amount of warm normal saline solution was injected into the femoral vein, as a result of which the heart rate decreased to 18 in 10 seconds; stimulation of the saphenous now caused the rate to increase to $26\frac{1}{2}$ beats, but after the stimulation it returned to 18.

Repeated stimulation, or sometimes a single stimulation of a sensory nerve, tends to cause permanent (*i. e.* permanent for the individual experiment) changes in the heart rate. Thus, if the heart is beating slowly, two or three stimulations of a sensory nerve may cause an acceleration of the heart which continues for hours, or as long as the experiment continues; simply ligating the sciatic nerve has caused a similar effect. If, on the other hand, the heart is beat-

ing rapidly, repeated stimulations may cause the rate to become and remain slow.

These are further illustrations of the already mentioned tendency of the heart to reach and remain at a constant rate, whenever its rate has been changed.

The afferent nerve fibres by which reflex acceleration is produced.

—Attention has already been called to the part which the condition of the cardio-inhibitory centre plays in determining whether reflex acceleration or reflex slowing of the heart follows stimulation of afferent nerves: in this section some facts relating to the afferent nerve fibres themselves will be discussed.

Aside from such nerves as the depressors and vagi, which are known to contain nerve fibres having special relations to the vasomotor and respiratory centres, there is evidence that there are different kinds of afferent nerve fibres in other nerve trunks.

In a previous paper, for example, I have collected evidence based on experiments of Howell and others and of my own which tends to show that in most mixed nerve trunks there are two varieties of nerve fibres which may influence the vasomotor centre, one causing a reflex rise, the other a reflex fall of blood pressure.¹ These results suggest the question whether those nerve fibres, stimulation of which causes a reflex acceleration of the heart, will, under different circumstances (when, for example, the condition of the cardio-inhibitory centre has been altered), cause a reflex slowing, or whether, in fact, there are two sets of nerve fibres, stimulation of one of which will always cause an acceleration, provided it has any effect at all upon the heart rate, while stimulation of the other set will cause a slowing. Further, what is the relation of the nerve fibres which cause reflex changes in the heart rate to those which cause changes in the blood pressure?

In the historical review given at the beginning of this part of the paper evidence was stated that stimulation of some nerves (*e. g.* the trigeminus) nearly always causes a reflex slowing of the heart, whereas stimulation of certain other nerves (*e. g.* the sciatic) more frequently causes an acceleration, or an acceleration first and then a slowing. I have observed in my own experiments that when the saphenous and the sciatic were stimulated in the same animal the former usually caused only an acceleration, while the latter frequently caused an acceleration followed by a slowing; moreover, slowing

¹ HUNT: *Journal of physiology*, 1895, xviii, p. 381.

alone occurred more frequently from stimulation of the sciatic than of the saphenous. Since this difference of action of the various nerves was observed in experiments in which there was no reason for supposing that the condition of the cardio-inhibitory centre was different in one case from its condition in the other, the most probable explanation is that there are two varieties of nerve fibres involved, and that one variety occurs in larger number in some nerves than does the other variety.

The fact also that stimulation of such a nerve as the sciatic has or may have a twofold action upon the heart, causing first a reflex acceleration and then a slowing,¹ suggests that there are two sets of fibres involved, and that the action of one set becomes evident before that of the other.² Such a double effect upon the heart is never, or only very rarely, observed when certain other nerves, such as the depressor or trigeminus, are stimulated.

Working upon this supposition, many experiments were performed in the hope of finding a method by which the conductivity or irritability of one set of fibres might be suspended while that of the other remained. The methods employed were in general the same as those which I employed to separate physiologically those nerve fibres which cause a reflex fall of blood pressure from those which cause a rise, and consisted essentially in subjecting the nerve trunks to influences which altered their conductivity or irritability, and then observing the effect upon the heart rate of stimulating them in various ways; of course precautions were taken to avoid causing, at the same time, changes in the cardio-inhibitory centre. Some of the methods employed, although giving evidence of the existence of two sets of fibres to the vasomotor centre, gave only negative results as to the afferent fibres to the cardio-inhibitory centre; one, however, the experiments on the regeneration of nerves, gave positive results.

Effect of stimulating the central end of a recently regenerated nerve.

—Most of these experiments were performed upon the sciatic nerves of cats. One nerve was crushed by drawing a ligature tightly around

¹ If, as is often the case, a rise of blood pressure also occurs from stimulation of the sciatic, this may be the cause, in part, of the slowing of the heart; the latter often occurs, however, when there is no change in the blood pressure, and also when there is a fall of blood pressure.

² Cf. MELTZER: *Archiv für Physiologie*, 1892, p. 390 (afferent nerves to the respiratory centre); also my paper on afferent nerve fibres to the vasomotor centre, *op. cit.*, p. 406.

it, high in the thigh; the wound was closed and the nerve allowed to regenerate. After a period of five or six weeks, or after signs of motion became apparent for some distance down the leg, the animals were anæsthetized (usually by cerebral compression), both sciatics exposed and divided, and the central ends stimulated with tetanizing currents of varying intensities. Six experiments were performed in this manner, and in all of them stimulation of the regenerated nerve produced a different effect upon the heart rate from that caused by stimulating the normal nerve. Stimulation of the former usually caused an acceleration of the heart; in some cases no effect was produced, but in none was there a reflex slowing. Stimulation of the normal nerve in these animals caused in all cases a reflex slowing.

One of these experiments was as follows.

Experiment 32. Cat. Left sciatic crushed 42 days previously. Anæsthesia caused by cerebral pressure. Blood pressure 100 mm. of mercury. Stimulation of the left sciatic about $1\frac{1}{2}$ inches below point of injury, with currents of varying strength, caused a very slight acceleration of the heart; in one case, for example, the rate increased from 27 to 29 in 10 seconds, the blood pressure remaining unchanged. Stimulation of the right (normal) nerve caused only reflex slowing; during one stimulation, for example, the rate decreased from $27\frac{1}{2}$ to 20 in 10 seconds, while the blood pressure fell 2 mm. of mercury.

The results of the above experiment differ from those usually observed in that stimulation of the nerves in this case caused no change in the blood pressure, whereas stimulation of the normal nerve usually causes a rise, and stimulation of the regenerated nerve a fall, of blood pressure. The absence of any changes in the blood pressure in this experiment makes it improbable that blood pressure changes were the cause of the difference in the effect upon the heart rate in the other experiments; there is, moreover, other evidence for this view. Thus, if an unusually long interval be allowed to elapse between the crushing and the stimulation of the nerve, the power of a portion of the nerve near the point of injury to cause a reflex fall of blood pressure may be lost, while that to cause acceleration remains. Thus, in one experiment 48 days were allowed to elapse between the operation and the stimulation of the nerves; the result was that stimulation of the nerve at a certain distance from the point of injury caused a rise of blood pressure, while the heart rate was increased from 18 to 24 beats in 9 seconds. Also, on the other

hand, stimulation of the normal nerve may occasionally cause a fall of blood pressure, although a reflex slowing of the heart occurs.

I think the above considerations show sufficiently clearly that the changes in the heart rate are independent of the changes in the blood pressure.

The most probable explanation of the result of these experiments is that in such mixed nerve trunks as the sciatic, there are two sets of afferent nerve fibres to the cardio-inhibitory centre, one of which causes inhibition, the other stimulation, of this centre, and that in a nerve which has been crushed the former regenerates more rapidly than do the latter. Of course it is not necessary to suppose that the only function of these nerve fibres is to affect the cardio-inhibitory centre; they are probably ordinary sensory nerve fibres which can cause other reflexes, only some of them are connected with the vagus centre in such a way that their stimulation inhibits, while that of the other excites, this centre. What little evidence there is to connect either of these varieties of nerve fibres with other varieties (those causing changes in the vasomotor centre, for example) will be given below.

Effect upon cardiac reflexes of cooling the afferent nerve. — One of the simplest ways of separating physiologically the nerve fibres, stimulation of which causes a reflex rise of blood pressure from those which cause a fall, is to cool the nerve trunk and then stimulate it below the point of cooling; the reflex vaso-constrictors lose their conductivity at a higher temperature than do the reflex vasodilators. My experiments so far have failed to show any difference in the action of cold upon the fibres causing a reflex slowing and those causing a reflex acceleration of the heart. Cardiac reflexes, whether acceleration, slowing, or the two combined, as a rule have disappeared at about the temperature (10° C. or less) at which a reflex rise of blood pressure was no longer obtained; when the cooling was continued below this point stimulation of the nerve caused a fall of blood pressure but no effect upon the heart rate.

Effect of varying the strength and rate of stimulation. — My observations upon these points were confined almost exclusively to experiments upon the sciatic of the dog. When stimulation of this nerve causes a reflex acceleration, there is usually a certain strength of current, varying in different cases, which gives the maximum acceleration, that is, causes the greatest number of additional heart beats. If the strength of the current is reduced below this optimum degree, the

maximum acceleration reached during stimulation may not at first be decreased, but the acceleration does not continue so long after the stimulation ceases; if, however, the strength of the stimulus is still further reduced, the maximum acceleration becomes less. When, on the other hand, the strength of the current is increased beyond the optimum, there may be at first a slight increase in the maximum acceleration reached, but this is followed by a greater tendency to slowing. This tendency to slowing becomes, as a rule, more and more marked as the strength of the current is increased, and sometimes stimulation produces only slowing; the latter result, however, is rather infrequent. As a rule, if there has been an acceleration with a weak stimulus, there is an equally great or greater acceleration with a stronger stimulus; the tendency to subsequent slowing is greater in the latter case.¹

As regards the strength of current necessary to cause reflex changes in the heart rate, as compared with the strength necessary to cause other reflex effects, it may be said that, in general, when the vagus is in tonic activity and the vasomotor centre is irritable, a stimulus too weak to affect the one is also usually without effect upon the other. Frequently neither the heart rate nor the blood pressure is influenced by a stimulus which causes respiratory and other reflex movements.

The results of stimulating a sensory nerve with a succession of induction shocks slowly repeated do not differ materially from those obtained with tetanizing currents; the only difference is that with the former method the acceleration or slowing is more slowly developed.

The above experiments and considerations seem to me to afford clear evidence for the view that there are two varieties of afferent nerve fibres to the cardio-inhibitory centre, one causing an excitation and the other an inhibition of this centre. The mere fact that in the same animal stimulation of one nerve may cause a reflex slowing and stimulation of another, a reflex acceleration of the heart, when the condition of the centre has undergone no change, is difficult to explain on any other hypothesis. Moreover, in the regeneration method we have a means of showing the presence of two sets of nerve fibres in the same nerve; when the nerve is crushed and

¹ Simanowsky is quoted (*Jahresbericht der Anatomie und Physiologie*, 1881, x, p. 62) as having observed that stimulation of the brachial and sciatic plexuses with a weak stimulus caused an acceleration, while a strong stimulus caused a slowing of the heart. MacWilliam (*Proceedings of the royal society London*, 1893, liii, p. 471) obtained similar results.

allowed to regenerate, those fibres causing an inhibition of the centre regenerate earlier than do those which cause an excitation. If the cardio-inhibitory centre underwent changes in irritability in the course of the experiment, it would be easy to see how stimulation of the same nerve fibres might in one case cause inhibition and in another excitation, just as the condition of the cerebral cortex or of the cardiac muscle is supposed to determine whether stimulation shall cause inhibition or augmentation; but in the above experiments changes in the centre were excluded.

We have, further, no evidence that stimulation of the one set of fibres can ever under any circumstances cause any change but a reflex slowing, or stimulation of the other set anything but a reflex acceleration of the heart.

Although, as was shown above, the condition of the cardio-inhibitory centre plays an important part in determining the manner in which this centre responds to the stimulation of a mixed nerve, such as the sciatic, yet this influence is limited to determining whether the centre responds to the impulses reaching it along the one or the other set of fibres; in other words, when both sets of fibres are stimulated inhibition or increased action will result according as the centre is more irritable to the one or the other set of impulses.

The relation which these fibres to the cardio-inhibitory centre bear to other nerve fibres — those to the vasomotor centre, for example — is an interesting but very complex problem. The experiments on regenerating nerves suggested at first that the fibres which cause a reflex fall of blood pressure are identical with those causing a reflex acceleration of the heart. The experiments on the effect of cold upon the nerves, however, show that the two sets of fibres cannot be identified in this manner, for cold causes the fibres which produce reflex changes in the heart rate to lose their conductivity earlier than those which cause a fall of blood pressure.

For a similar reason it seems impossible to identify the fibres which cause a rise in blood pressure with those which cause a slowing of the heart.

Of course the relative irritability of the cardio-inhibitory and vasomotor centres probably exerts an important influence in this matter, and a more thorough investigation may show the following view to be incorrect, but at present it is difficult to avoid the conclusion that we are dealing with four varieties of nerve fibres: (1) those causing a reflex rise of blood pressure, (2) those causing a reflex fall of blood

pressure, (3) those causing a reflex slowing of the heart, and (4) those causing a reflex acceleration of the heart. These four varieties of nerve fibres are very unequally distributed in different nerve trunks, some being entirely absent from certain of them. Thus there is no satisfactory evidence that there are fibres in the depressor which ever cause a reflex rise of blood pressure,¹ or that the saphenous of the cat contains any fibres which can cause a fall;² as has already been pointed out, stimulation of the trigeminus, if it has any effect upon the heart, always causes a slowing, and v. Cyon³ found only an acceleration to result from stimulation of the third root of the depressor. The glossopharyngeal usually causes a fall of blood pressure and a slowing of the heart, the infraorbital⁴ a rise of blood pressure and a slowing of the heart, while stimulation of the sciatic may cause either a rise or a fall of blood pressure and either a slowing or an acceleration of the heart.

PART III.

GENERAL CONSIDERATION OF RESULTS.

Functions of the accelerator nerves. — In speaking of the functions of the accelerator nerves it is necessary to distinguish the effect which these nerves have upon the rate from their effect upon the force of the heart-beat. It is well known that these two effects have no constant relation to each other; in fact they seem almost always to occur separately. Thus in very few of my own experiments in which acceleration of the rate has been observed has there been any evidence that the force of the beats has been increased; a rise of blood pressure was exceptional, and when present bore absolutely no relation to the increase in the rate. Although the same observation has been recorded by almost every one who has worked upon this subject, the statement is still frequently made that the increase in the heart rate leads to a rise of blood pressure.

On the other hand, in those experiments in which increase in the force of the heart-beat has been found to follow stimulation of

¹ See v. CYON: *Archiv f. d. ges. Physiol.*, 1898, lxx, p. 229.

² HUNT: *Journal of physiology*, 1895, xviii, p. 386.

³ v. CYON: *op. cit.*, p. 142.

⁴ KNOLL: *Sitz.-Ber. d. kais. Akad. d. Wiss., math.-naturw. Cl.*, 1885, xcii, 3, p. 449.

the accelerators there has been as a rule little or no acceleration of the rate. Thus in my own experiments when a rise of blood pressure occurred it usually resulted from stimulation of the accelerators of the left side, and as I have already shown these nerves have, as a rule, but little effect upon the heart rate. It is interesting that in the experiments which Roy and Adami,¹ who studied the effect of the accelerators upon the force of the heart-beat very carefully, quote to show the effect of direct stimulation of these nerves upon the heart, there is a marked increase in the force of the heart while there is scarcely any change in the rate.

Such facts as the above have led to the suggestion that there are really two kinds of nerve fibres in the accelerator nerves: one which causes increase in the rate, and another which causes an increase in the force of the beat. The former variety may be called the accelerator, the latter the augmentor nerve fibres.

The function of the augmentor fibres is doubtless to cause a rise of general blood pressure, or, as Roy and Adami² put it, "they sacrifice the heart in order to increase the output of the organ and enable the ventricles to pump out their contents against heightened arterial pressure."

The principal functions which can be ascribed to the nerve fibres which cause an increase in the rate of the heart with no effect upon the blood pressure have been referred to already when their tonic activity and relation to the vagi were discussed. From the experiments on the effects of cutting these nerves two conclusions may be drawn: (1) the normal rate of the heart is determined in part by the impulses constantly reaching it through these nerves, (2) in cases in which the irritability of the heart is low, the tonic activity of these nerves plays an important part in maintaining the regular rhythm of the heart. Attention was also called to the fact that the accelerator centres and nerves are very resistant to influences (low blood pressure, extreme asphyxia, certain drugs, etc.) which quickly depress other nerve centres and even affect the cardiac muscle itself; hence these nerves, in virtue of their tonic activity, are in a posi-

¹ ROY and ADAMI: *Philosophical transactions*, 1892, 183 B, p. 244, see curve 14, p. 239, stimulation of left annulus, and curve 15, p. 241. In most of the experiments upon which these authors base their views of the effect of the accelerators upon the force and output of the heart acceleration was produced reflexly by the stimulation of a sensory nerve; as has been shown above it is very improbable that the acceleration in such cases was due to the accelerator nerves at all.

² ROY and ADAMI: *op. cit.*, p. 296.

tion to supply an efficient stimulus to the heart when one is most needed.

It was shown further that the tonic activity of these nerves limits the action of the vagi; when the heart is slowed by reflex stimulation of the vagus, not only do the accelerators limit the extent of the slowing, but they enable the heart to return more quickly to its normal rate. It is probable that this action of the accelerators is very important in counteracting influences which cause reflex slowing of the heart, such, for example, as injury to the abdominal viscera, and perhaps also in asphyxia.

Nothing definite can be said as to the part the accelerators play when they are thrown into increased activity, as so little is known about the conditions under which this occurs; in fact, little can be added to the statements made by the brothers Cyon more than thirty years ago. These physiologists, who recognized that there is not necessarily an increase in the work done when these nerves are stimulated, suggested that their function consisted in diminishing the resistance which the vagi opposed to the development of the heart-beat.

Although the total amount of work done by the heart when it is accelerated by stimulation of these nerves is not increased (the work being simply differently distributed in time, as the Cyons expressed it), yet, as has been already shown, this acceleration causes fatigue of the heart; perhaps this fatigue is due to the shortening of the periods during which the heart is at rest. In what manner either the heart itself, or the rest of the body, benefits by the more rapid rate (which of itself causes fatigue of the heart) is obscure.

Possibly some clue to this problem is to be found in the work on the transfusion of blood through isolated organs. It has become the generally recognized view that in such experiments much better results are obtained when the stream of blood is supplied intermittently¹ than when it is supplied at a constant pressure. If the blood is supplied under constant pressure, cedema and other pathological changes appear in the organ under experiment,² and the circulation is soon slowed, or even arrested altogether; this is due in part to the cor-

¹ Although Kronecker, in 1871, stated that less injury is done to the vessels of a muscle by high pressure if this is intermittent than when it is constant. Stevens and Lee (Studies from the biological laboratory, Johns Hopkins University, 1884, iii, p. 109) seem to have been the first actually to make use of an intermittent supply of nutrient fluid in transfusion experiments.

² HAMEL: *Zeitschrift für Biologie*, 1889, xxv, p. 492.

puscles adhering to the walls of the blood vessels and to each other,¹ and even a great increase in the pressure causes but a temporary improvement. If, however, the blood is supplied intermittently, the slight movement of the corpuscles at each pulsation and the consequent changes in the diameter of the blood vessels prevent this clumping together of the corpuscles, and the transfusion can be continued for a much longer time at a comparatively low pressure.²

I have been unable to find any statements as to the number of pulsations per minute which yield the best results in transfusion experiments; this number would probably be influenced by such factors as the nature of the blood-vessel walls, the length of the capillaries, etc., so that it is very probable that a rate which is suitable for one organ would not be adapted to another. Support for this supposition is found in v. Cyon's work on the circulation through the thyroid gland:³ v. Cyon showed that when the heart was beating slowly, as a result of stimulating the vagus, a much greater amount of blood flowed from the thyroid vein than when the heart was beating more rapidly, although the blood pressure was the same and vasomotor changes in the gland were excluded; the outflow from the saphenous vein was also increased, but relatively to a much less degree than that from the thyroid vein.

In the light of such experiments as the above it seems quite probable that conditions may arise under which the circulation of an organ may be better provided for by a series of rapid heart-beats, each of which throws out a smaller quantity of blood, than by a slower rate with which the output at each beat is greater. In fact certain changes in the respiratory waves of the curve of blood pressure resulting from the stimulation of the accelerator nerves seems to point to such an action. One of the most constant effects upon the blood pressure curve of stimulating the accelerator nerves is a marked increase in the amplitude of the respiratory undulations; this occurs not only when the blood pressure rises or remains at the same level, but also when it falls; and further, it occurs in animals under curare and in which artificial respiration is maintained by a pump or pair of bellows which discharges with great regularity the same amount of

¹ VON FREY: *Archiv für Physiologie*, 1885, p. 538. Welch and Mall consider that the absence of pulsation in an occluded artery plays an important part in the production of a hæmorrhagic infarction.

² JACOBI: *Archiv f. exper. Pathol. u. Pharmacol.*, 1890, xxvi, p. 398.

³ v. CYON: *op. cit.*, p. 161.

air at each stroke. If changes in both the blood pressure and the volume of the respired air are excluded, as is the case in such experiments as these, then the increased amplitude of the respiratory waves seems to indicate that a larger volume of blood is passing through the lungs at any given time, and this, in turn, that a larger amount of blood is being returned to the right auricle through the systemic vessels. Of course the increased amplitude of these waves may have been due in part to the faults of the mercury manometer, that is, when the heart was beating more slowly the excursions of the column of mercury were increased so greatly by its inertia that the respiratory undulations were obscured, whereas with the more rapid rate the effects of the mercury's inertia were less marked. But it does not seem probable that this change in the respiratory waves can be explained entirely in this manner, for not only are these waves often marked when the heart is beating slowly, but their amplitude is frequently increased by injecting a large amount of normal saline solution into the circulation, although no changes occur in the blood pressure and heart rate, or at least do not occur for some time after the changes in the respiratory waves. The increased amplitude of these waves after the injection of normal saline solution is almost certainly due to the larger amount of liquid in the vessels of the lungs; the same change occurring after stimulation of the accelerators is probably due to a similar cause.

Finally the experiments of Stevens and Lee upon the action of intermittent pressure upon the blood vessels of the frog and terrapin suggest the possibility that the accelerators may, at times, play a part in maintaining the normal tone of the blood vessels. These authors found that "a rhythmically interrupted force applied to the blood vessels of the frog and terrapin through the medium of a circulating fluid exerts a special action upon them, in consequence of which a constriction of them takes place;" as a result of such action a much smaller amount of liquid supplied intermittently is needed to maintain a given arterial pressure than when the force is a constant one. No experiments were made to determine the number of interruptions which give the best results; it is probable, however, that this number would be found to differ in the case of the vessels of different organs, so that in some a rapid, in others a slow, rate would have the more marked effect.

Rapid heart action of other than reflex origin. — There are many cases of rapid heart action of other than reflex origin upon which

the experiments described in this paper may throw some light; a few such cases will be considered briefly.

Voluntary acceleration of the heart. — The power which some persons have of voluntarily increasing the heart rate has been studied with especial care by Tarchanoff¹ and Pease,² and more recently by Van de Velde.³

Tarchanoff made a number of experiments in order to determine the cause of the acceleration, *i. e.* whether it is due to a diminution of the tonic activity of the vagi or to a stimulation of the accelerators; he reached the conclusion that the acceleration is due to a direct action upon the centres of the accelerator nerves. The grounds for this conclusion were three: (1) the manner in which the acceleration appeared and disappeared, (2) the changes in the form of the sphygmograms, and (3) the changes in the volume of the extremities. Tarchanoff found that in the person upon whom he experimented, the maximum acceleration was reached only after one half to three quarters of a minute after the beginning of the effort to increase the heart rate; the return to the normal rate was also gradual. Comparing the slow development of the voluntary acceleration with the rapid development following the section of the vagi, Tarchanoff drew the conclusion that the voluntary acceleration was due to the accelerator nerves. It does not seem to me that this argument is at all conclusive. It does not seem fair to compare the effect of section of the vagi, which causes an immediate effect on the heart rate, with the acceleration following a distinct effort of the will.⁴

It has also been shown above that under certain circumstances the diminution of the tonicity of the vagus caused by the stimulation of a sensory nerve may be very slowly developed and very slowly disappear. Moreover, in one of Van de Velde's patients the maximum acceleration occurred in the first 10 seconds of the effort; whereas Böhm in experiments upon animals found from the examination of a large number of tracings that when the accelerators were stimulated directly the maximum acceleration occurred as a rule in the second

¹ TARCHANOFF: *Archiv f. d. ges. Physiol.*, 1885, xxxv, p. 109.

² PEASE: *Boston medical and surgical journal*, 1889, cxx, p. 526.

³ VAN DE VELDE: *Archiv f. d. ges., Physiol.*, 1897, lxvi, p. 232.

⁴ Van de Velde compares the effort necessary to cause acceleration to the feeling experienced when a person attempts to perform some unusual muscular movement, such, for example, as contracting the muscles of the ear, or flexing independently the last phalanx of the finger.

10 seconds of the stimulation. In the experiments of Pease also the latent period seems to have been very short; thus in some of the tracings given the first beat after the effort was made seems to have been shortened and the greatest acceleration to have occurred in the first two or three seconds, the entire effort continuing but five seconds. We certainly have no reason to suppose that the accelerators can be thrown into activity by an act of the will more quickly than when they are stimulated directly by the electric current.

It is also worthy of note that in the case of Salomé, upon whom most of Tarchanoff's experiments were made, acceleration of the heart easily resulted from slight external causes, — a fact which, judging from experiments upon animals, points to an unstable condition of the cardio-inhibitory centre.

The second argument which Tarchanoff brings forward in support of his view — the changes in the form of the sphygmogram — seems to me to be still less conclusive, owing to the difficulty of interpreting these curves; in fact the changes which Tarchanoff adduces as evidence that the increase in the heart rate was due to the action of the accelerators are very nearly the same as those which Nothnagel brought forward to show that in some cases of rapid heart action the increase comes from a diminution of the vagus tonus.

The third argument of Tarchanoff in support of the above view is that when the heart rate increased, the volume of the foot, as determined by the plethysmograph, was not increased, although, according to Tarchanoff, an increased volume would necessarily have occurred as a result of the augmented blood pressure if the acceleration in rate had been due to a diminution of vagus tonus; it is however, by no means uncommon for section of the vagi to cause acceleration of the heart without any increase in the blood pressure occurring — in fact there is sometimes a fall of general blood pressure.

In the light of these considerations it seems to me that the evidence for the view that voluntary acceleration is due to the action of the accelerator nerves is entirely inconclusive; in fact I am inclined to think that the weight of evidence is rather in favor of the view that it is due to a diminution of the tonus of the vagi.

Acceleration of the heart during muscular exercise. — The influence of the cardiac nerves on the increase in the heart rate during muscular exercise has been most carefully studied by Hering.¹ This author

¹ HERING, H. E. : Archiv f. d. ges., Physiol., 1895, lx, p. 429.

reaches the conclusion that the acceleration is due in part to an increased activity of the accelerator nerves, perhaps of reflex origin, and in part to a diminution of the tonic activity of the vagi caused by the increased respiratory movements.

It seems to me that a careful examination of Hering's experiments shows that the diminution of the tonic activity of the vagi is sufficient to explain his results, and that there is no clear evidence for believing in any increased action of the accelerators; the tonic activity of the latter nerves plays, however, a very important part here, as in the acceleration following stimulation of sensory nerves. Without going into too many details, the following observation on Hering's experiments may be made. The average rate of the heart reached during muscular exercise in a number of experiments was 320 beats per minute, whereas the average rate during rest after section of the vagi was 321. Moreover, in one half of these experiments (see table p. 440) the maximum rate reached during exercise was less than or just the same as the rate in rest after the vagi were cut; in the other half of these experiments the maximum acceleration in exercise after the vagi were cut was less than 7 per cent. This acceleration of 7 per cent may have been due to a stimulation of the accelerator nerves, but it should be observed (1) that in other experiments (p. 476) in which both the vagi and accelerators had been cut a much greater acceleration (33 per cent and more) — due probably to changes in the respiration and blood pressure — was observed, and (2) that direct stimulation of the accelerators after section of the vagi may cause a much greater increase in the heart rate; the Cyons, for example, obtained an acceleration of over 50 per cent in such experiments.

On the other hand Hering's results show very clearly that the acceleration of the heart rate in exercise was much less after section of the accelerators; the average acceleration was but two-fifths as great as when they were intact. I think, however, that this difference can be attributed entirely to the removal of the tonic impulses of the accelerators. That the accelerators were in tonic activity in these experiments is made almost certain by the fact that when the vagi were cut after section of the accelerators there was but a slight increase in the heart rate; the greatest increase was 60 and the average 31 beats per minute, whereas in another series of experiments in which the vagi alone were cut the average increase was 122 beats and the smallest increase (and this was a very exceptional case)

was 68.¹ It seems to me that these results, so far as the influence of the cardiac nerves is concerned, can be explained in exactly the same way as the acceleration following stimulation of a sensory nerve, namely, the essential factor in the acceleration is a diminution of the activity of the cardio-inhibitory centre; if the accelerator nerves are intact and in tonic activity the maximum rate reached is greater than when they are not in activity, but there seems to be no sufficient evidence for supposing that these nerves are thrown into increased action in muscular exercise.

Athanasiu and Carvallo² have also recently studied this question, and reached the conclusion that the essential factor in the acceleration is the reflex diminution of the activity of the cardio-inhibitory centre; their tracings also show that the latent period of the acceleration in muscular exercise is very short.

MacWilliam,³ who believes the acceleration to be of vagus origin, has called attention to the fact that in those animals which are capable of long continued muscular exercise (such as the horse, dog, and hare) the vagi are in a condition of marked tonic activity, while in such an animal as the rabbit, which is not capable of so prolonged exertions, the tonic activity of the vagi is not so marked.

Acceleration following compression of the carotids. — Cooper and Magendie stated that acceleration of the heart results from the compression of the carotid; this subject has been studied with especial care by François-Franck,⁴ who considered acceleration to be due to a stimulation of the accelerator nerves. Examination of the curves and the descriptions of the experiments of François-Franck show that in most cases the vagi were intact; in other cases nothing is said about the vagi. The curves published by this author are strikingly like the curves of reflex acceleration obtained by stimulating a sensory nerve after section of the accelerators; the second, and in some cases the first, heart-beat after compression of the carotid was shortened, and after the compression ceased the heart returned instantly to its previous rate or was slowed, the very first beat being

¹ Hering commented on the slight increase in the heart rate following section of the vagi after previous section of the accelerators, and recognized that the integrity of these nerves is an important factor in the acceleration following section of the vagi, but he seemed to hesitate to interpret his results as evidence for the tonic activity of the accelerators. (See also note on p. 397.)

² ATHANASIU and CARVALLO: *Archives de physiologie*, 1898, p. 561.

³ MACWILLIAM: *Proceedings of the royal society*, London, 1893, liii, p. 476.

⁴ FRANÇOIS-FRANCK: *Travaux du laboratoire de Marey*, 1878-79, p. 74.

either of the normal length or prolonged. François-Franck noted the very short latent period as compared with the latent period when the accelerator nerves are stimulated electrically, and suggested that the difference may be due to the normal stimulus from the central nervous system acting differently from direct electrical stimulation; but there seems to be no evidence for this supposition. It is true that François-Franck states that no acceleration occurred after extirpation of the inferior cervical and first thoracic ganglia; but such an operation, unless performed with great care, destroys the tonicity of the vagus centre.

Many more cases of acceleration of the heart in which diminution of the tone of the vagi is probably the chief factor might be cited. Thus the acceleration accompanying each act of deglutition in man,¹ that occurring during each inspiration,² and the increase in the heart rate when the lungs are inflated by a pair of bellows,³ all seem to be due to a diminution of the tonic activity of the vagi. The cause of the rapid heart rate observed in certain diseases,⁴ and after the admin-

¹ MELTZER: *Archiv für Physiologie*, 1883, p. 223.

² FREDERICQ: *Archives de biologie*, 1882, iii, p. 86.

³ HERING: *Sitz.-Ber. d. kais. Akad. d. Wiss., math.-naturw. Cl.*, 1871, lxvi, 2, p. 348. See also H. E. HERING: *Archiv f. d. ges. Physiol.*, 1895, lx, p. 461.

⁴ The rapid heart action in paroxysmal tachycardia is sometimes referred to a diminution of the tonus of the vagus, sometimes to a stimulation of the accelerators; there seems to be little unanimity of opinion among those who have described this condition. The above experiments upon animals seem adapted to throw some light upon this subject. Unless we assume that the accelerator nerves of man are very different physiologically from those of the lower animals, it seems impossible to accept the view that in some cases of tachycardia the rapid rate of the heart is due to a stimulation of the accelerator nerves. Thus there are cases reported (by H. C. Wood, *e. g.* *University medical magazine*, 1890-91, iii, p. 273, and by Hochhaus, *Deutsches Archiv für klinische Medizin*, 1893, li, p. 19) in which the rapid action of the heart ended instantaneously, the rate decreasing in one case from 184 to 78 per minute; experiments on animals show that stimulation of the accelerators is always followed by a long after-effect upon the heart. Again, the rapid action of the heart in these cases may continue for days, the heart beating continuously at double or more than double its normal rate; such an acceleration in animals can be maintained for but a very short time by powerful electrical stimulation of the accelerators.

On the other hand, many of these cases can be easily explained by the diminution of the tonus of the inhibitory nerves. I have shown above how easy it is to get the cardio-inhibitory centre into a condition of unstable equilibrium by the action of drugs, changes in blood pressure, respiration, etc.; I have also called attention to the fact that there are great individual variations, the centre being inhibited in some animals with ease, in others of the same species with difficulty. When the cardio-inhibitory centre is in such a condition of unstable equilibrium, very slight

istration of drugs, is in many cases obscure; but there seems as yet to be no evidence inconsistent with the view that in these cases the action is, as a rule, either a direct one upon the heart itself or upon the cardio-inhibitory centre.

Unusual difficulties are met with in investigating the effect of psychical influences upon the heart rate, but there seems to be no reason for supposing that the acceleration in such cases is different in origin from that in the cases which have been discussed above.

Leaving out of consideration the cases in which the cause of the acceleration is doubtful, and admitting that in some of those discussed above the acceleration is due in part to a direct action of the accelerator nerves, it must still be granted that decrease of the tone of the cardio-inhibitory centre is the most usual cause of an increase in the heart rate.

When it is remembered what an important part inhibition in one form or another plays in other functions of the body, — how, for example, it seems to occur in every act of respiration,¹ in every movement of a limb,² how important it is in movements of the pupil,³ the regulation of the flow of the blood, the movements of the intestine,

causes — a little ether or curare, weak stimulation of a nerve, a little operating, etc. — are sufficient to cause a marked acceleration of the heart; this acceleration may continue for a long time. If we assume that in the patients who suffer from paroxysmal tachycardia the cardio-inhibitory centre is in an unstable condition (usually as an individual peculiarity, though this condition seems to be exaggerated at times by such influences as recent illness, excessive use of alcohol, coffee, etc.), it is easy to see how some slight change might bring on an attack. Among the exciting causes mentioned (see Pröbsting, *Deutsches Archiv für klinische Medizin*, 1882, xxxi, p. 349, and Herringham, *Edinburgh medical journal*, 1897, i, p. 367) are sudden exertions or injuries, digestive and uterine disturbances — influences which might readily cause a reflex inhibition of the vagus centre. In some cases pathological changes of the pericardium and of the myocardium are described; in the light of the experiments of Knoll upon the reflexes from the heart it is not improbable that such changes can cause a reflex inhibition of the cardio-inhibitory centre. That diminution of the tonic influence of the vagi is sufficient to account for the rapid heart observed in most cases of tachycardia follows from the effects of injuries to the trunk of the vagi; Eddinger says that a heart rate of 240 per minute and more has resulted in man from such injuries — a rate which is not often exceeded in paroxysmal tachycardia.

¹ MELTZER: *Archiv für Physiologie*, 1892, p. 340.

² HERING and SHERRINGTON: *Archiv f. d. ges. Physiol.*, 1897, lxviii, p. 222. SHERRINGTON: *Journal of physiology*, 1899, xxiii, suppl., p. 26.

³ BRAUNSTEIN: *Zur Lehre von der Innervation der Pupillenbewegung*, 1894, p. 95.

etc.,¹ it is not surprising that the body should make use of it in regulating the rate of the heart-beat. Not only can an increase in the heart rate be caused more quickly by an inhibition of the cardio-inhibitory centre than by a stimulation of the accelerator centre, but it probably involves a smaller expenditure of energy. Although the accelerator nerves take no direct part in the production of a more rapid heart-beat (*i. e.* they are not thrown into increased activity), yet it is largely in virtue of their tonic activity that inhibition of the vagus centre leads to such prompt results.

Whether an inhibition of the accelerators leading to a slowing of the heart ever occurs is not known. It is not improbable, however, that changes in the tonicity of the accelerator centre occur, the tonicity being at one time increased and at another decreased, but there seems to be no evidence that such changes are ever produced suddenly, for example, as a result of a reflex act.

SUMMARY OF RESULTS.

The chief facts brought out in this paper may be summarized as follows:—

(1) The accelerator nerves of the dog, cat, and rabbit, and probably of other mammals, are almost always in tonic activity; the tonic activity of the accelerators is not impaired by influences which abolish not only the tonic activity but also the irritability of many other nerve centres.

(2) Under some circumstances the tonic activity of the accelerators is an important factor in maintaining the normal rhythm of the heart, and stimulation of them will sometimes cause an irregular heart to become regular; this action of the accelerator seems to be most marked in cases in which the irritability of the cardiac muscle has been reduced in some manner.

(3) Stimulation of the accelerators, if excessive, will decrease the rate of beat, and make the heart more irritable to impulses reaching it through the vagi. Even death may result from the excessive stimulation of these nerves.

These facts indicate that the stimulation of the accelerators can cause real fatigue of the cardiac muscle.

(4) New evidence is afforded for the view that the inhibitory and accelerator nerves are strictly antagonistic; this antagonism applies to

¹ For other illustrations of inhibition, see MELTZER: *Archiv für Physiologie*, 1883, pp. 225–235.

both systole and diastole, but with the same strength of current the systole is more easily influenced by stimulation of the accelerators, and the diastole by stimulation of the inhibitory nerves.

(5) The tonic activity of the accelerators limits the tonic activity of the inhibitory nerves, and *vice versa*; the normal heart rate, so far as this is governed by the extra-cardiac nerves, is determined by the impulses reaching it simultaneously through these two channels.

(6) The inhibitory nerves exert a protective influence over the heart; not only do they restrain the action of the accelerators, but their stimulation seems to improve the condition of the heart.

(7) The view that reflex acceleration is caused by inhibition of the cardio-inhibitory centre is confirmed; no evidence could be found that the accelerator nerves are ever thrown into action reflexly.

(8) The tonic activity of the accelerator nerves exerts a modifying influence over reflex acceleration; the maximum acceleration is greater, and is longer continued, and there is less tendency to a subsequent slowing when these nerves are intact.

(9) There are probably in most nerve trunks two varieties of nerve fibres to the cardio-inhibitory centre; one variety causes an inhibition, the other an excitation of this centre. When a nerve is crushed the former variety regenerates earlier than the latter.

(10) The most important functions of the accelerators seem to be connected with their tonic activity; aside from this their functions are obscure, but it is not improbable that by altering the rate of the heart-beat they exercise an important influence upon the circulation through certain organs.

(11) It is very probable that almost all cases of rapid heart action are due to a diminution of the tonic activity of the cardio-inhibitory centre.

